Interleukin-6 Production in a Murine Model of *Pneumocystis carinii* Pneumonia: Relation to Resistance and Inflammatory Response

WANGXUE CHEN,1,* EDWARD A. HAVELL,1 FRANCIS GIGLIOTTI,2 AND ALLEN G. HARMSEN1

Trudeau Institute, Inc., P.O. Box 59, Saranac Lake, New York 12983,1 and Departments of Pediatrics and Microbiology and Immunology, University of Rochester School of Medicine, Rochester, New York 146422

Received 3 August 1992/Accepted 8 October 1992

The production of interleukin-6 (IL-6) and its possible relationship to host resistance and inflammatory response to *Pneumocystis carinii* infection were examined in mice with severe combined immunodeficiency (SCID mice). IL-6 activity was detected in the serum and lungs of *P. carinii*-infected mice but not in mice free of *P. carinii*. Moreover, the IL-6 levels in *P. carinii*-infected mice increased markedly after spleen cell reconstitution but then decreased to an undetectable level after the clearance of *P. carinii*. However, neutralization of IL-6 activity in spleen cell-reconstituted SCID mice by treatment with anti-IL-6 immunoglobulin G (IgG) resulted in no significant effect on the clearance of *P. carinii* (*P > 0.05*). Both the serum and lungs of treated mice contained an excess amount of anti-IL-6 IgG and lacked detectable IL-6. These results suggest that failure to inhibit the *P. carinii* clearance by anti-IL-6 treatment was not due to insufficient administration of antibody or incomplete neutralization of IL-6 activity. However, compared with mice receiving rat control IgG, mice treated with anti-IL-6 IgG had significantly higher numbers of neutrophils and lymphocytes (particularly CD8+ cells) in the lung lavage fluids (*P < 0.05 for both*) at day 19 after reconstitution. In addition, the levels of both total IgG (*P < 0.001*) and *P. carinii*-specific antibodies (*P < 0.05*) in the serum of mice treated with anti-IL-6 were significantly higher than those in control mice. These results indicate that although *P. carinii* infection causes both local and systemic production of IL-6 in SCID mice, IL-6 does not appear to play a crucial role in the clearance of *P. carinii*. However, it appears that during resolution of *P. carinii* pneumonia, IL-6 plays a role in the regulation of pulmonary inflammation and antibody responses.

*Pneumocystis carinii* pneumonia (PCP) is a major cause of morbidity and mortality in AIDS patients, whereas it rarely occurs in immunocompetent hosts (22). The mechanisms of this susceptibility in AIDS patients are poorly understood. Previous studies have shown that resistance to *P. carinii* is CD4+ T lymphocyte dependent (13, 26, 34). Results of our recent studies show that proinflammatory cytokines (tumor necrosis factor alpha [TNF-α] and interleukin-1 [IL-1]) play a crucial role in this CD4-dependent resistance (4, 5). However, the importance of other cytokines is unknown.

IL-6 is a proinflammatory cytokine produced by a variety of lymphoid and nonlymphoid cells and has several immune regulatory functions similar to those of TNF and IL-1 (20, 25). Like TNF and IL-1, IL-6 participates in the host response to a variety of infectious and inflammatory stimuli, including bacterial pneumonia, persistent viral infection, and endotoxemia (11, 16, 19, 21, 36). In addition, IL-1 and TNF are important mediators in the induction of IL-6 mRNA expression and protein synthesis, and IL-6 down-regulates TNF and IL-1 production (1).

Evidence to date has suggested that IL-6 is involved in the immunopathogenesis of opportunistic infections, including *P. carinii* infection. Abnormal IL-6 mRNA expression and protein secretion has been reported in human monocytes and macrophages infected with human immunodeficiency virus type 1 (31) as well as in human immunodeficiency virus-infected patients (3). Human immunodeficiency virus-infected human macrophages (18), but not alveolar macrophages from normal rats (17), increase both IL-6 mRNA expression and protein secretion in response to *P. carinii* in vitro. However, the importance of IL-6 in *P. carinii* infection in vivo is not clear.

The objective of the present study was to investigate the local and systemic IL-6 responses to *P. carinii* infection in mice with severe combined immunodeficiency (SCID mice) (13, 24) and to determine the importance of endogenous IL-6 in clearance of *P. carinii* and pulmonary inflammation during the resolution of PCP. Evidence from this study suggests that IL-6 responses occurring during the resolution of PCP are not important in the clearance of *P. carinii* organisms but are involved in down-regulation of pulmonary inflammation.

MATERIALS AND METHODS

**Mice.** C.B-17 +/+ and C.B-17 scid/scid (SCID) mice 6 to 8 weeks old were obtained from the Trudeau Animal Breeding Facility. A foundation stock of SCID mice was originally obtained from Leonard Schultz of Jackson Laboratory, Bar Harbor, Maine. They were bred and housed in microisolator cages containing sterilized food and water and were shown to be free of most common pathogens (13). SCID mice in this colony spontaneously develop detectable *P. carinii* infection at about 4 weeks of age, and the resistance to the infection can be adoptively transferred by reconstitution of the animals with spleen cells from immunocompetent mice (4, 5, 13). Clearance of the organism from infected lungs is completed by day 19 after reconstitution.

**Assessment of *P. carinii* infection.** The intensity of the *P. carinii* infection in mouse lungs was determined by counting the number of *P. carinii* nuclei by a previously described method (6) with a slight modification (13). In brief, the lungs

* Corresponding author.
were pushed through a stainless steel screen into Hanks' balanced salt solution (GIBCO, Grand Island, N.Y.), and the resulting suspension was diluted for preparing smears with a cytocentrifuge. The smears were stained with Diff-Quik (Baxter, Miami, Fla.), and the number of *P. carinii* nuclei per 10 to 30 oil immersion fields was counted. This number was used to calculate the total *P. carinii* nuclei per lung. With this method, 10^4-10^6 nuclei per lung represented the limit of detection.

**Reconstitution of SCID mice with immunocompetent spleen cells.** Spleens were collected aseptically from 6- to 8-week-old C.B-17/+ mice, diced into small pieces, gently pushed through a stainless steel screen into Hanks' balanced salt solution, and triturated with a Pasteur pipette. After the debris was removed, the cells were washed twice with phosphate-buffered saline (pH 7.2; Sigma, St. Louis, Mo.), counted, and resuspended in phosphate-buffered saline at a concentration of 5 x 10^6 nucleated cells per ml. Recipient SCID mice (herein referred to as reconstituted SCID mice) were given 1 ml of the cell suspension by injection into a tail vein.

**Kinetics of in vivo IL-6 production.** Groups of four reconstituted SCID mice were killed at the time of reconstitution (day 0 postreconstitution [DPR 0]) or at predesignated time points as indicated in Fig. 1. In addition, four *P. carinii*-free unreconstituted SCID mice were used to determine the baseline of IL-6 production. The mice were anesthetized and bled by cardiac puncture, and the serum was collected. After the bleeding, the mice were killed and the lungs were removed and processed for the IL-6 assay. Sera and lung suspensions for the IL-6 assay were stored at −70°C until used. Sera from mice killed at the same time were pooled and diluted 1:8 with RPMI 1640 (GIBCO) before use. Lung suspensions were thawed, homogenized with a motorized Teflon pestle, and centrifuged at 10,000 × g and 4°C for 30 min. The supernatant was carefully decanted and sterilized by filtration (0.22-µm-pore-size filter) before being assayed.

**IL-6 bioassay.** The IL-6 contents of tested samples were assayed by monitoring the ability of the samples to cause proliferation of the IL-6-dependent murine hybridoma cell line B9 (2, 16). The IL-6 titer (units per milliliter) was defined as the reciprocal of the highest dilution of the test sample that induced a half-maximal proliferative response of B9 cells. In each assay, an internal laboratory IL-6 standard that was calibrated in terms of an 88/514 interimmunofluorescence standard (specific activity, 6.5 x 10^9 U/mg of protein; obtained from the Biological Response Modifiers Program, National Cancer Institute, Frederick, Md.) was included. The limit of detection in the assay was 20 U per lung and 4 U/ml for undiluted serum. Selected samples were also assayed for IL-6 activity in the presence of a monoclonal antibody against IL-6 (MP5-20F3) to ensure the specificity of assay (data not shown).

**Treatment of reconstituted SCID mice with anti-IL-6 IgG.** The monoclonal antibody against IL-6 is a rat-mouse hybridoma (MP5-20F3) that secretes a rat immunoglobulin G1 (IgG1) capable of neutralizing murine IL-6 (27). The hybridoma was grown as ascites in the peritoneal cavities of pristane-primed CB6F1 mice. The antibody was purified by precipitation with caprylic acid and ammonium sulfate (20%) and resuspended in pyrogen-free saline. Detailed descriptions of this antibody and its activities in vivo and in vitro were reported previously (23, 27). The anti-IL-6 neutralizing titer (neutralizing units [NU] per milliliter) was defined as the reciprocal of the highest IgG dilution that, when reacted with an equal volume of a test sample with 20 U of IL-6 per ml, neutralized 50% or more of the proliferation activity on B9 cells. Recipient mice were given intraperitoneal injections of 2 x 10^6 NU of pure anti-IL-6 IgG or equal amounts (equal protein concentrations) of control rat IgG (Sigma) in 0.2 ml of pyrogen-free saline. The endotoxin levels in anti-IL-6 IgG and rat control IgG, as determined by chromogenic *Limulus* amebocyte lysate test (Whittaker Bioproducts, Walkersville, Md.), were 220 and 185 endotoxin units per ml, respectively. The numbers of animals used and the treatment regimes are detailed in Table 1. All mice were killed on DPR 19, and the numbers of *P. carinii* nuclei in their lungs were determined.

In one of the duplicated experiments, the lungs were lavaged (12) 24 h before being processed for *P. carinii* nuclear counts. This type of lavage procedure does not markedly alter the number of *P. carinii* nuclei per lung in *P. carinii*-infected mice (unpublished data). Lavage cells were counted in a hemacytometer, and differential cell counting was done by examination of cell smears produced with a cytocentrifuge and stained with Diff-Quik. Lymphocyte phenotypes in the lungs of mice from different treatment groups were analyzed with a FACSscan cytofluorometer (Becton Dickinson, Sunnyvale, Calif.). Cells were stained with fluorescein isothiocyanate-conjugated F(ab')2 fragments of anti-Thy-1.2 (30H12), anti-CD4 (OK15), anti-CD8 (TIB-210), and anti-mouse immunoglobulin (Cappel Laboratories, Westchester, Pa.) as described elsewhere (13, 15).

**Measurement of *P. carinii* specific antibody and total serum IgG.** Antibodies specific for *P. carinii* were detected by a standard enzyme-linked immunosorbent assay. Flat-bottom microtiter plates (Flow Laboratories, McLean, Va.) were coated with either mouse *P. carinii* surface glycoprotein A (1:10 dilution) (10) or a soluble total protein preparation from the lungs of *P. carinii*-free SCID mice (10 µg of protein per ml). For the preparation of lung protein, the lungs were first homogenized and sonicated. After centrifugation, each supernatant was removed and filtered through a 0.45-µm-pore-size filter, and the protein was quantified with a commercial kit (Bio-Rad, Richmond, Calif.). Test sera

---

**Table:**

<table>
<thead>
<tr>
<th>Exp</th>
<th>Treatment</th>
<th>No. of <em>P. carinii</em> nuclei</th>
<th>No. of mice with undetectable <em>P. carinii</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Unreconstituted controls</td>
<td>6.78 ± 0.10</td>
<td>0/4</td>
</tr>
<tr>
<td></td>
<td>Spleen cell reconstituted</td>
<td>&lt;3.98 ± 0.00</td>
<td>4/4</td>
</tr>
<tr>
<td></td>
<td>+ control rat IgG</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Spleen cell reconstituted</td>
<td>4.31 ± 0.33</td>
<td>1/4</td>
</tr>
<tr>
<td></td>
<td>+ rat anti-IL-6 IgG</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(2 x 10^6 NU)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Unreconstituted controls</td>
<td>6.04 ± 0.12</td>
<td>0/4</td>
</tr>
<tr>
<td></td>
<td>Spleen cell reconstituted</td>
<td>&lt;3.98 ± 0.00</td>
<td>4/4</td>
</tr>
<tr>
<td></td>
<td>+ control rat IgG</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Spleen cell reconstituted</td>
<td>5.34 ± 0.79</td>
<td>2/4</td>
</tr>
<tr>
<td></td>
<td>+ rat anti-IL-6 IgG</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(2 x 10^6 NU)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Reconstitution was done with immunocompetent spleen cells on DPR 0.
* Data are log10 means ± standard errors of the means (n = 4). The limit of detection of *P. carinii* nuclei was 10^4 nuclei per lung.
* Treatment reagents were given intraperitoneally on DPR 4, 8, and 12.
* Data are log10 means ± standard errors of the means (n = 4). The limit of detection of *P. carinii* nuclei was 10^4 nuclei per lung.
* Treatment reagents were given intraperitoneally on DPR 4, 8, and 12.
were diluted 1:100 in phosphate-buffered saline containing 0.05% Tween 20 (Sigma). Controls for this assay included a monoclonal antibody (90-3-2B5) specific for mouse P. carinii glycoprotein A (10), mouse hyperimmune sera produced by immunizing immunocompetent mice with subcutaneous injections of P. carinii preparations and Freund’s complete adjuvant (Difco, Detroit, Mich.), and normal mouse sera. Total IgG levels in serum were measured by a commercial radial immunodiffusion assay kit (ICN, Costa Mosa, Calif.) according to the manufacturer’s instructions.

Statistical analysis. Data are presented as means ± standard errors of the means of results calculated from animals with the same treatment. Differences in the observations made between the groups of mice with different treatments were analyzed by using the Mann-Whitney U test, Student’s t test, or one-way analysis of variance followed by a post hoc least significant difference pairwise comparison test, when appropriate (35). The difference was considered significant if P was <0.05.

RESULTS AND DISCUSSION

IL-6 production during the resolution of PCP. The amounts of IL-6 in the serum and lungs of P. carinii-infected SCID mice killed at progressive times post-reconstitution (DPR 0 to 19) are presented in Fig. 1. Small but substantial amounts of IL-6 were present in the serum and in the lungs of SCID mice infected with P. carinii at the time of reconstitution (DPR 0). In contrast, no IL-6 was detected in either the serum (<32 U/ml) or the lungs (<20 U per lung) of SCID mice that were free of P. carinii. Reconstitution of P. carinii-infected SCID mice with immunocompetent spleen cells significantly increased both local (in the lung) and systemic (in the serum) IL-6 activity. This activity peaked on DPR 7 at 1,384 U/ml in the serum and 7,601 ± 2,011 U per lung and remained at about this level until DPR 15 (Fig. 1). The amounts of IL-6 in both the serum and the lungs then declined rapidly at the end of the experiment (DPR 19), when the infection was cleared, to a level comparable to that in the lungs of P. carinii-free SCID mice (undetectable levels, i.e., <32 U/ml in serum and <20 U per lung).

The bioassay used to measure the IL-6 level in the present study could be interfered with by possible cytokine inhibitors present in the samples, and the values of IL-6 detected might not represent the actual amounts of IL-6 produced; nevertheless, the presence of IL-6 in the lungs and the serum of P. carinii-infected SCID mice (Fig. 1) but not in those of P. carinii-free SCID mice suggests that IL-6 was produced both locally and systemically in response to P. carinii infection in immunocompromised hosts. Thus, IL-6, like TNF and IL-1, is produced during P. carinii infection. However, the pattern of production is different for these three cytokines. TNF is present only during the resolution of PCP (4), whereas both IL-6 (Fig. 1) and IL-1 (5) levels increase with reconstitution and decrease with the clearance of the organism. In addition, IL-1 and TNF are present only in the lungs (4, 5), whereas IL-6 was found both in the lungs and in the circulation. These findings suggest that TNF and IL-1 function principally at the site of infection, whereas IL-6 has the potential to act systemically.

Anti-IL-6 IgG treatment does not inhibit the clearance of P. carinii. To determine whether endogenous IL-6 is important in resistance to P. carinii, groups of four reconstituted SCID mice were treated with either rat anti-IL-6 IgG or rat control IgG. Intraperitoneal injection of anti-IL-6 into reconstituted SCID mice on DPR 4, 8, and 12 (Table 1, experiment 1) or at 2 h before reconstitution and on DPR 4, 8, and 12 (experiment 2) had no significant effect on the number of P. carinii nuclei seen on DPR 19, compared with results obtained with reconstituted SCID mice that had received control rat IgG (all P > 0.05, Table 1), although in one experiment there was a trend toward diminished P. carinii clearance in two of four mice that received anti-IL-6 treatment. To determine the efficacy of anti-IL-6 treatment, IL-6 and anti-IL-6 IgG levels in the serum and lungs of three reconstituted, P. carinii-infected SCID mice that had been treated with anti-IL-6 were determined. IL-6 was not detected in either the serum (<4 U/ml) or the lungs (<20 U per lung) of mice that received anti-IL-6 IgG on DPR 4 and were killed on DPR 8. Indeed, at this time IL-6 reached its peak level in reconstituted SCID mice that had not been treated with the antibody (Fig. 1). Furthermore, there were excess amounts of IL-6 neutralization activity in both the serum (801.3 ± 434 U/ml) and the lungs (5,464.3 ± 2,782.4 U/ml per lung) of these mice. Therefore, results of the present study suggest that, unlike TNF and IL-1, when endogenous IL-6 is neutralized with specific antibodies, there is no significant effect on host defense against P. carinii.

Like IL-1 and TNF-α, IL-6 mediates a wide array of immunologic activities (20, 25). Therefore, it seems reasonable to assume that IL-6 may play a role in resistance to P. carinii. This assumption is further enforced by the appearance and maintenance of high IL-6 levels in both the serum and the lungs of P. carinii-infected SCID mice after reconstitution and its rapid decrease in concordance with P. carinii clearance. However, there is no compelling published evidence, to the best of our knowledge, for the protective effects of endogenous IL-6 in experimental infections. Although IL-6 is produced locally and systemically in bacterial, viral, and parasitic infections (11, 16, 19, 21, 36), its role in host defense against pathogen infection is currently unclear. For example, sublethal Listeria monocytogenes infection in mice induces IL-6, IL-1, and TNF production in the infected organs (14–16), but administration of exogenous IL-6, unlike that of exogenous IL-1 and TNF, shows no beneficial effect (7). Neither does exogenous IL-6 treatment have any beneficial effect on the protection of mice from experimental Pseudomonas aeruginosa infection (33). Circumstantial evidence and studies of treating animals with exogenous IL-6 in other infection models to date show that IL-6 can be protective of (9), deleterious to (27, 36), or have no effect on (7, 11) resistance. It is also interesting that IL-6 is an
important growth factor for *Mycobacterium avium* (8). Taken together, these data indicate that the presence of IL-6 during the process of certain infections may not be directly associated with host resistance to that infection.

**Effect of anti-IL-6 IgG treatment on pulmonary inflammation and *P. carinii*-specific antibody production.** Previous studies in this laboratory have shown that spleen cell reconstitution of *P. carinii*-infected SCID mice induces a profound pulmonary inflammation (4, 5, 13). IL-6 is believed to be able to stimulate hematopoietic stem cell growth and macrophage differentiation (20, 25) and has recently been shown to modulate the pathogenesis and course of *Chlamydia trachomatis* pneumonia in mice (19). Therefore, it was deemed to be of interest to compare the total and differential cell counts in the lung lavage fluids of anti-IL-6 IgG-treated mice with those of mice treated with control IgG on DPR 19 (Table 2). Mice treated with anti-IL-6 IgG had significantly higher numbers of total cells, neutrophils, and lymphocytes in the lung lavage fluids than did control animals (all *P* < 0.05). The prominent pulmonary inflammation in anti-IL-6-treated animals was also evident histologically. Flow cytofluorometric analysis of lung lavage lymphocytes showed that anti-IL-6-treated mice had greater numbers of CD4+ and CD8+ cells than did control mice, although the difference was only significant for CD8+ cells (Fig. 2). This difference was also seen in lung interstitial lymphocytes; the proportion of CD8+ cells was significantly higher in anti-IL-6-treated mice than in control rat IgG-treated animals (23.77% versus 7.36%; *P* < 0.05). In contrast, there was no difference in the number of immunoglobulin-positive lymphocytes either in the lung lavage fluids (Fig. 2) or in the lung interstitium (11.01% versus 9.70%).

The types and the numbers of inflammatory cells accumulating in the lungs of either anti-IL-6-treated mice or mice receiving control rat IgG in the present study are comparable to those reported in our previous studies of PCP in SCID mice (4, 5, 13). Therefore, the statistically higher numbers of inflammatory cells seen in anti-IL-6-treated mice on DPR 19 is most likely due to the protraction of pulmonary inflammation initiated in the early stage of the resolution. This suggests a potential role for IL-6 in the down-regulation of pulmonary inflammation during the resolution of PCP. IL-6 is important in down-regulation of endotoxin-induced acute pulmonary inflammation, presumably by a TNF-α- and IL-1-mediated mechanism (32). The potential of IL-6 in down-regulation of inflammation is further evident in a recent study of murine experimental endotoxemia, in which the peak serum IL-6 level is in concordance with the lowest numbers of total peripheral blood leukocyte counts (29). Since the submission of this report, it was reported that IL-6 inhibits the proliferation of macrophage progenitors and differentiated macrophages (23a). Moreover, treatment of mice suffering from hypersensitivity pneumonitis with anti-IL-6 caused a strong, sustained neutrophilic response, with a lung free cell number that was significantly higher than that in control mice (7a). However, the actual mechanism of possible IL-6-dependent down-regulation of pulmonary inflammation observed in the present study is not known.

Because IL-6 participates in the maturation of activated B cells into immunoglobulin-secreting plasma cells (20, 25), it is reasonable to expect that anti-IL-6-treated mice might show reduced production of *P. carinii*-specific antibodies, total serum IgG, or both. The data presented in Table 3, however, refute this assumption. Compared with the serum of control mice, the serum of anti-IL-6-treated mice had significantly higher levels of both total IgG (*P* < 0.001) and specific antibodies to *P. carinii* glycoprotein A (*P* < 0.05). The reason for the discrepancy between previously published results and our results on the regulation of antibody production by IL-6 is not clear. However, it is possible that the function of IL-6 in regulating antibody responses varies with the nature of infections or the principal target organs. For example, in experimental murine cerebral malaria the serum malaria-specific antibody levels are 25% higher in mice treated with anti-IL-6 IgG than in control mice (11), whereas in experimental lymphocytic choriomeningitis virus infection specific antibody levels are positively correlated with IL-6 levels (21). In this regard, it is interesting that mice treated with anti-IFN-γ show enhanced specific antibody

### Table 2. Cellular profiles of lung lavage fluids of anti-IL-6 IgG-treated, *P. carinii*-infected SCID mice on DPR 19

<table>
<thead>
<tr>
<th>Mice</th>
<th>No. of cells (10^6/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
</tr>
<tr>
<td>Unreconstituted controls</td>
<td>2.38 ± 1.23</td>
</tr>
<tr>
<td>Reconstituted SCID</td>
<td></td>
</tr>
<tr>
<td>Control IgG treatedb</td>
<td>10.75 ± 2.55</td>
</tr>
<tr>
<td>Anti-IL-6 IgG treatedd</td>
<td>23.13 ± 3.40</td>
</tr>
</tbody>
</table>

a Data are means ± standard errors of the means for four mice.

b Treatment regents were given intraperitoneally 2 h before reconstitution and on DPR 4, 8, and 12.

c *P* < 0.05 versus control rat IgG-treated mice (Student’s t test).

d *P* < 0.01 versus control rat IgG-treated mice (Student’s t test).

![Figure 2](http://iai.asm.org/Downloaded from http://iai.asm.org on October 29, 2017 by guest)
TABLE 3. Effect of anti-IL-6 IgG treatment on serum antibody levels of P. carinii-infected and reconstituted SCID mice on DPF 19

<table>
<thead>
<tr>
<th>Specific antibodies to P. carinii glycoprotein a</th>
<th>Total IgG (mg/dl)</th>
<th>No. of animals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unreconstituted controls</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum IgG-treated</td>
<td>0.025 ± 0.004</td>
<td>&lt;30.0</td>
</tr>
<tr>
<td>Anti-IL-6 IgG-treated</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum IgG treated</td>
<td>0.088 ± 0.024</td>
<td>68.19 ± 10.17</td>
</tr>
<tr>
<td>Anti-IL-6 IgG treated</td>
<td>0.402 ± 0.310</td>
<td>137.50 ± 8.18</td>
</tr>
</tbody>
</table>

a Data are means ± standard errors of the means compiled from two experiments with similar results.

ACKNOWLEDGMENTS

We thank Joyce Reome, Jean Brennan, and Lynn Stiles for their help in part of this study.

This work was supported by Public Health Service grants AI-28354, AI-23544 and AI-23302 from the National Institutes of Health.

REFERENCES