Reversal of Neutropenia With Intravenous Gammaglobulin in Autoimmune Neutropenia of Infancy


Intravenous gammaglobulin (IVIgG) was used to treat autoimmune neutropenia of infancy in two males with repeated infections. The neutrophil count increased significantly in both patients with the initial IVIgG therapy; 1 patient went into remission. The neutrophil count in the other remained above baseline for 3 wk, and a subsequent booster infusion also caused the neutrophil count to increase. The patients have remained clinically well since their treatment began. Serial studies of antineutrophil antibody and serum lysozyme, performed to elucidate the mechanism of action, suggested decreased neutrophil destruction, perhaps by Fc receptor blockade, as well as decreased synthesis of antineutrophil antibody. Neutrophil function was not impaired after the neutrophil count increased. Many patients with immune neutropenia have a benign course, but those who have significant infections could be treated, acutely or prophylactically, with intravenous gammaglobulin.

AUTOIMMUNE NEUTROPENIA of infancy appears to be one of the more common forms of neutropenia in childhood. The syndrome is characterized by a severe neutropenia, usually recognized between the ages of 5 and 7 mo. In general, most patients are asymptomatic, but skin infection, pneumonia, or fungal diseases may develop. The neutropenia is self-limited, and recovery occurs usually within 1–3 yr. Cell-bound neutrophil antibodies, mostly IgG, are demonstrated by a direct immunofluorescence assay. Circulating antibodies may also be found, some with specificities for the known neutrophil antigens. Bone marrow aspiration reveals normal differentiation of the three cell types, with an absence of the most mature myeloid elements (bands or segmented cells).

Intravenous gammaglobulin (IVIgG) has been used in the treatment of idiopathic thrombocytopenic purpura (ITP) of childhood and induces a significant increase in the platelet count in most cases. One mechanism of action that has been well documented in these patients is inhibition of Fc-receptor-mediated clearance, as assessed by increased half-life of radiolabeled IgG anti-D-coated autologous red blood cells after IVIgG treatment. This inhibition persisted for approximately 4 wk. It is presumed that the destruction of antibody-coated platelets is also slowed during this interval, allowing for an increase in the platelet count. Other postulated mechanisms include: reduction in autoantibody synthesis, clearance of persistent viral antigens from circulation, and “protection” of megakaryocytes and/or platelets from the autoantibodies. No definite evidence exists to support any of the latter three mechanisms.

None of the proposed mechanisms of action discussed above imply any specificity of the IVIgG for ITP, and this therapeutic approach may prove applicable to the treatment of any immune hematocytopenia. One adult with autoimmune neutropenia was treated with IVIgG infusions with a resulting dramatic increase in the absolute neutrophil count that lasted for 1 mo; increases in the neutrophil count were also seen after subsequent single-dose infusions. This article describes the treatment with IVIgG of two male infants with autoimmune neutropenia of infancy. A peak absolute neutrophil count greater than 3,000/cu mm was reached in each case after the initial IVIgG therapy, and the neutrophil counts remained elevated above baseline for 2–3 wk; elevation of the neutrophil count was also seen after a single booster infusion in one of these patients.

The intravenous gammaglobulin infused was IgSRK or Sandoglobulin. It is a gammaglobulin preparation made from Cohn fraction II of plasma treated at pH 4 in the presence of traces of pepsin to render it suitable for intravenous use. No side effects were noted with IgSRK therapy.

CASE REPORTS

Patient 1 is a 14-mo-old male of Hispanic origin who was the product of a normal pregnancy and delivery. At the age of 6 mo, neutropenia was discovered when he became febrile due to a urinary tract infection. He was treated with intravenous antibiotics; the neutropenia persisted and did not respond to a trial of 2 mg/kg/day of prednisone given for 2 wk. Over the next 4 mo he was hospitalized twice for fever and neutropenia. On one occasion, his neutrophil...
count was greater than 1,000/cu mm, but otherwise it was always less than 200/cu mm. Biochemical profile, antinuclear antibody, serum immunoglobulins, and lysozyme determinations were all within the normal range. Bone marrow aspiration performed at diagnosis revealed a normal morphology with the exception of a few mature myeloid forms; cyogenetic analysis and colony-forming units-granulocyte were normal. Both direct immunofluorescence (using the patient’s paraformaldehyde-treated neutrophils) and indirect immunofluorescence (using the patient’s serum and a panel of paraformaldehyde-treated neutrophils from normal donors) for neutrophil-specific antibodies were positive with the use of fluorescein-conjugated rabbit anti-human IgG; no reaction was detected with the anti-IgM antibody. The specificity of the neutrophil antibody detected in the patient’s serum by the indirect immunofluorescence test could not be determined. Leukoaagglutinins were not demonstrable. Swiss Red Cross gammaglobulin, 500 mg/kg, was given intravenously on 3 successive days, and a single dose of 500 mg/kg was given 3 wk later.

Patient 1 was a 13-mo-old white male who was well until 9 mo of age, when he developed chronic diarrhea; severe neutropenia was discovered at this time. Bone marrow aspiration was normal, except that relatively few mature forms of the myeloid series were seen; the direct and indirect immunofluorescence test for antineutrophil antibodies gave positive reactions with anti-IgG, but no specificity could be determined. Leukaegglutinins were not found. Antinuclear antibodies and serum immunoglobulins were within the normal range. The diarrhea persisted and the patient’s weight decreased from 22 to 16 pounds; he was admitted to the hospital for central line placement and total parenteral alimentation. Intestinal biopsy revealed chronic jejunitis and rota virus was identified in stool specimens. After several weeks, the diarrhea abated and oral feeding was gradually reinstalled. He became febrile, and a blood culture was found to contain Candida albicans. He received three doses of amphotericin-B, 2 doses of intravenous Swiss Red Cross gammaglobulin, 450 mg/kg/day, and his central line was then removed. He became afebrile, continued to tolerate oral feeding, and his neutrophil count increased to greater than 3,000/cu mm. He remained clinically well and was discharged from the hospital 10 days later.

RESULTS

The dramatic rise in the neutrophil count with IVIgG is depicted in Fig. 1; the peak neutrophil count in both patients was greater than 3,000/cu mm attained within 7 days of the IVIgG infusions. In patient 1, the neutrophil count decreased to baseline over 3 wk, and a single booster infusion was given, with a subsequent peak neutrophil count of 832/cu mm. Patient 2 has maintained a neutrophil count of greater than 1,000/cu mm since treatment. No other change in the complete blood count was seen.

The results of serial neutrophil antibody testing in both patients are shown in Table 1. After IVIgG therapy, direct immunofluorescence remained positive in patient 1, even when the neutrophil count was 3,800/cu mm. However, on one occasion after the booster infusion, the direct immunofluorescence test became negative, but it became positive again 1 wk later. The serum antineutrophil antibody became undetectable 2 wk after the first dose of IVIgG, and remained undetectable on 3 subsequent tests. This patient’s neutrophils were typed during the IVIgG-induced remission and were found to be NA1, NA2, NB1 positive, and NC1 negative. Patient 2 had a diminution in his neutrophil-associated IgG after IVIgG treatment; his serum IgG antineutrophil antibody continued to be weakly positive. There were no red cell, platelet, or lymphocyte antibodies detected before or after the IVIgG was administered.

White cell function testing was evaluated at the time of the peak neutrophil count after the booster infusion (patient 1). A qualitative nitro blue tetrazolium reduction test (NBT) and myeloperoxidase staining were normal. Chemotaxis of the neutrophils in a Boyden Chamber was normal, as was the ability of the patient’s serum to support the chemotaxis of normal white blood cells. Lysozyme determinations were made before the initial infusion, before the single booster, and were compared to specimens obtained at the time of the peak neutrophil counts in patient 1. No changes in these lysozyme values were observed. Serum IgG measured in patient 1 increased from 1,100 mg/dl to 2,150 mg/dl after the initial 3 IVIgG infusions.

Table 1. Results of Neutrophil Antibody Testing by Direct and Indirect Immunofluorescence in Patients 1 and 2

<table>
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<th>Date</th>
<th>Direct</th>
<th>Indirect</th>
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IgSRK was given on 5/24/82 to 5/26/82 and on 6/14/82 to patient 1 and on 7/30 and 7/31 to patient 2.
No fever or clinical illness has been seen over the 3 mo of this therapy in either patient, in marked contrast to the frequent fevers (patient 1) and severe illness (patient 2) detected previously.

DISCUSSION

IVIgG produced significant increases in the neutrophil count in these two cases of autoimmune neutropenia of infancy. Patient 1 had had no response to a 2-wk course of prednisone. Treatment of the two patients with IVIgG was not continued because both patients are well; the increase in the neutrophil count was transient in patient 1 and has persisted for 5 mo in patient 2.

The mechanism of action of the IVIgG in elevating the neutrophil count is unclear. Temporary inhibition of reticuloendothelial monocyte-macrophage Fc-receptor function, which might slow the rate of antibody-coated neutrophil destruction, is suggested by the persistence of neutrophil-associated antibody in patient 1 when the neutrophil count increased and by the rapid decline of the neutrophil count after therapy in both patients. The failure to demonstrate a decrease in the serum lysozyme when the neutrophil count increased, as might be expected if the rate of neutrophil destruction diminished, is most likely attributable to the lack of specificity of elevated lysozyme as a marker of neutrophil destruction as well as the fact that the lysozyme levels were normal prior to the initiation of IVIgG therapy.

A contribution to the effect of the IVIgG by decreased antineutrophil antibody synthesis is suggested by the decrease in antineutrophil antibody activity seen in both patients. The serum antineutrophil antibody in patient 1 became undetectable after the initial IVIgG therapy, and the neutrophil-associated IgG became transiently negative after the booster dose. Patient 2 had a decrease in neutrophil-associated IgG after IVIgG, coincident with the onset of clinical remission. The change in serum antibody in patient 1 and in neutrophil-associated antibody in patient 2 could have been coincident with a spontaneous improvement of the immune neutropenia. However, the transient disappearance of the neutrophil-associated antibody in patient 1, as well as the decrease in antineutrophil antibody in both patients, argues strongly for an effect of the IVIgG on decreasing the synthesis of antineutrophil antibody.

The demonstration of normal neutrophil function at the time of the peak neutrophil count after the booster dose in patient 1 is consistent with the patients' clinical improvements after IVIgG therapy and suggests that the IVIgG did not interfere with neutrophil function.

Most infants with autoimmune neutropenia do not require treatment, but those who do are at a significant disadvantage, since immunosuppression, i.e., steroid therapy, may further worsen their immune deficit, as would have been the case in patient 2 with a documented fungal infection. Furthermore, steroids increase the neutrophil count partly by preventing egress of neutrophils from the vascular space. The nontoxic use of high-dose intravenous gammaglobulin appears to be an effective therapy in autoimmune neutropenia of infancy, and further trials are clearly warranted.

REFERENCES


3. Lalezari P: Natural history of autoimmune neutropenia of infancy (in preparation)


Reversal of neutropenia with intravenous gammaglobulin in autoimmune neutropenia of infancy

J Bussel, P Lalezari, M Hilgartner, J Partin, S Fikrig, J O'Malley and S Barandun