Immunoglobulin therapy in infectious disease

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The role of immunoglobulin therapy in the prevention and treatment of infectious disease has been greatly expanded by the ability to administer immunoglobulins intravenously. Neonates, patients with AIDS, and bone marrow transplant recipients are beneficiaries of the advances being made in IgG therapy. Studies suggest that the synergistic effect of a combination of antibiotics and antibodies will be useful in the future. Other future directions for antibody therapy include development of monoclonal antibodies for treatment of sepsis. Also, clinical trials of monoclonal antibody against tumor necrosis factor are setting the stage for monoclonal antibody research directed increasingly to the anti-mediator concept.

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THE ABILITY to render immune serum globulin safe for intravenous use will increase the potential role of immunotherapy in treating infectious disease. As originally developed for clinical use, immune serum globulin was highly concentrated and easily stored. The fractionation procedure, however, resulted in aggregates of immunoglobulin G (IgG). When given intravenously, these clumps of IgG activated complement to cause an anaphylactoid response. Immune serum globulin was restricted, therefore, to intramuscular (IM) use, which is limited by the pain threshold and the amount of muscle in a patient's flank. For the immunodeficient patient, monthly intramuscular injections of 100 to 150 mg/kg were barely adequate to achieve IgG levels in the normal range for even short periods.

In recent years, techniques have been developed to remove aggregates and produce a pure IgG solution. Reduction, enzyme reactions, acidification, and diethylaminoethyl (DEAE) column chromatography are some of the procedures capable of rendering IgG safe for rapid intravenous (IV) infusion in relatively high doses. These technologies have presented a remarkable array of potential new uses for immunoglobulins.

The rise in serum IgG produced by 100 mg/kg of IM globulin is about half that achieved by rapid IV infusion of the same dose. In addition, with the IV route, a progressive increase in dosage can produce even higher increments in the serum IgG. Intravenous globulin doses of up to 500 mg/kg are now common; in some cases, such as for treatment of idiopathic thrombocytic purpura, doses as high as 1000 mg/kg have been used.

Occasionally, IV IgG will cause an acute reaction, such as phlebitis or hyperviscosity. Another concern

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with high IV doses of immunoglobulins is the potential for transmission of virus from the human plasma source. Plasma donors are screened for HIV and hepatitis B, but, until recently, screening for non-A, non-B hepatitis was not possible. The introduction of the hepatitis C test may identify additional potential hepatitis viruses, but this test still will not detect all non-A, non-B viruses.

Fortunately, transmission of non-A, non-B hepatitis has not been reported with any of the immunoglobulin products that are marketed in the United States (Gamimune N, Gammagard, Sandoglobulin, and Venoglobulin-I). Similarly, no cases of AIDS have been transmitted by immunoglobulin. However, certain immunoglobulin products in Great Britain and Sweden have been reported to cause non-A, non-B hepatitis in a small number of cases. The safety of the approved products in the United States is associated with the use of specific manufacturing techniques, such as acidification, that can kill the non-A, non-B hepatitis virus.

IMPORTANCE OF MEASURING SUBCLASSES

Human IgG is made up of four subclasses (IgG1, IgG2, IgG3, and IgG4), with different tertiary configurations and, presumably, different functions. For example, IgG1 plays a role in antiviral defense; IgG2, IgG3, and IgG4 are part of the respiratory defense against pneumococci and *Haemophilus influenzae*. IgG1 comprises approximately 60% of the total IgG; IgG2, about 29% to 30%; IgG3, about 6%; and IgG4, 4% to 5%. Measurement of either total IgG or of IgG1 can fall within the range of normal and mask a deficiency in one of the other subclasses. The workup of an immunodeficient patient, therefore, must include specific IgG subclass quantitation; this is readily available from reference laboratories.

Several studies confirm the importance of IgG subclass quantitation. At Washington University,[1] 7 of 30 children with recurrent sinopulmonary infections had IgG2-specific immunodeficiency. Yet, 4 of the 7 had normal IgG levels. At Boston Children's Hospital,[2] nine children with recurrent sinopulmonary infections and IgG2 deficiencies had almost monthly episodes of otitis media or sinusitis. In a prospective study, these IgG2-deficient patients were given 300 to 400 mg/kg of replacement immunoglobulin every 3 to 4 weeks for almost 1 year. The number of infections decreased dramatically during the study year. Thus, it appears logical to treat patients with subclass deficiency and recurrent infections with immunoglobulin replacement.

CLINICAL APPLICATIONS

Neonates

In the premature infant, immunoglobulin deficiency is a transient phenomenon related to the immature immunohumoral system. It has been suggested, therefore, that prophylactic IgG might prevent infectious complications in the premature infant. Since many of the infections in neonates are caused by *Staphylococcus epidermidis*, which is unrelated to humoral immunodeficiency, IgG may not be totally effective. On the other hand, neonatal sepsis caused by *Escherichia coli* and certain other pathogens is closely related to antibody defenses and might be susceptible to prophylactic treatment.

In a randomized study conducted in Italy,[3] premature, low-birth-weight infants who received globulin prophylaxis had significantly fewer infections and less septicemia than infants in the control group. The mortality rate also was lower, although the difference was insignificant. The usefulness of globulin prophylaxis in premature, low-birth-weight infants is now being tested in several large randomized studies in the United States.

Chronic lymphocytic leukemia

Studies conducted in the 1950s and 1960s suggested that patients with chronic lymphocytic leukemia (CLL) and hypogammaglobulinemia would not benefit from IM immune serum globulin prophylaxis. The advent of high-dose IV globulin therapy has dramatically changed the prognosis for these patients. A prospective randomized study of patients who had mild to profound hypogammaglobulinemia[4] demonstrated a significant reduction in bacterial infections among patients who received immunoglobulin prophylaxis.

Complications of bone marrow transplantation

The onset of graft vs host disease, cytomegalovirus (CMV) pneumonia, or bacterial infections are threats to successful bone marrow transplantation. A randomized study showed that prophylaxis with plasma from donors with high CMV titers could significantly reduce CMV symptomatic infection (mainly pneumonia) in bone marrow recipients.[5] A widely quoted study published in 1986, however, demonstrated no effect from globulin prophylaxis.[6] The study was small, used only CMV serum-negative

blood products, and included only transplant patients who were CMV serum-negative.

The significance of the controversial and variable results of these and other studies may be determined by a recent study.[7] In a Seattle hospital with 60 beds devoted to bone marrow transplantation, 350 patients were randomized to receive globulin prophylaxis, 500 mg/kg once a week for the first 3 months after transplantation, or to receive no prophylaxis. Among patients who received prophylaxis, the incidence of interstitial pneumonia decreased, the frequency of graft vs host disease was significantly reduced, and mortality unassociated with the primary malignancy was significantly reduced. Furthermore, a significant reduction in gram-negative sepsis and local infections was reported. Despite its high cost, most experts today consider globulin prophylaxis a major breakthrough in marrow transplantation.

AIDS and HIV-positive patients

Several potential uses of immunoglobulin exist for patients with acquired immune deficiency syndrome (AIDS). Continuous therapy with intravenous immunoglobulin will enable patients with HIV-associated thrombocytopenia to maintain platelet levels in the normal range. Immunoglobulin therapy also can help prevent opportunistic infections, particularly those caused by *Pneumococcus* and *H influenzae*. Children with HIV infections have a high incidence of recurrent bacterial infections. Among 71 pediatric AIDS patients seen at Bellevue Hospital in New York City over a period of 3.5 years, 38% experienced documented recurrent bacterial infections, with a mean of 4.8 episodes.[8] Most were bacterial respiratory infections caused by *Pneumococcus* or *H influenzae*. The higher mortality seen in the group that had the bacterial recurrent infection syndrome was not necessarily related to the bacteria, but to the identification of a more gravely ill population.

Although the authors of several studies have recommended globulin prophylaxis to stop the recurrent hospitalization from bacterial infections in children, most of the studies are small, uncontrolled, and anecdotal. An exception is a prospective study done in Scotland.[9] The study cohort consisted of eight pediatric patients with HIV infection and known recurrent bacterial infection syndrome. Globulin (200 mg/kg) was given every 3 weeks during the 1 year of observation. During the 12 months prior to the institution of globulin prophylaxis, the patients experienced a cumulative 220 days in the hospital, compared to a cumulative 56 days during the 12 months of globulin prophylaxis. The total number of serious infections in the 1 year prior to the study was 34, of which 13 were pneumonia. During the year of globulin prophylaxis, 6 serious infections occurred, including 4 episodes of pneumonia.

Two studies[10,11] have suggested that plasma from asymptomatic HIV-positive patients who have neutralizing antibodies to HIV will benefit patients with symptomatic AIDS. When symptomatic AIDS patients were infused with plasma from asymptomatic HIV-infected patients with neutralizing antibodies, the HIV antigen that was identified prior to infusion disappeared, both with a single infusion and with three monthly infusions. This approach is being explored in several ongoing randomized prospective studies.

COMBINATION THERAPY

In the future, a combination of antibiotics and antibodies may be shown to be beneficial in treating infectious diseases. Antimicrobial agents coupled with high-titered antibody against a given agent may have a synergistic effect. Several specific high-titered globulins have been developed, including those against *Pseudomonas aeruginosa*, group B streptococcus, pneumococci, *H influenzae*, and CMV—all infections for which modern chemotherapy alone may be insufficient.

Naturally occurring high antibody against *P aeruginosa*, for example, is present in approximately 1 of 20 persons, even though they have not had clinical pseudomonal infection. Screening plasma for antibody to this specific target pathogen can eventually form a pool of very high-titer *Pseudomonas* globulin, which can be fractionated.

The efficacy of the *Pseudomonas* hyperimmune globulin has been demonstrated in a controlled laboratory animal model.[12] Guinea pigs infected with *Pseudomonas* were treated with *Pseudomonas* globulin alone, tobramycin alone, or the combination of *Pseudomonas* globulin plus tobramycin. The findings led to a prospective study in human subjects. A double-blind, placebo-controlled, randomized trial of *Pseudomonas* hyperimmune globulin therapy is now underway in 130 intensive care unit patients with *Pseudomonas* pneumonia. The results of this study should reveal whether or not the addition of globulin to conventional therapy reduces mortality in the ICU.

CMV hyperimmune globulin combined with ganciclovir has led to survival rates greater than 50%

among patients with CMV pneumonia, and should have potential as therapy for bone marrow transplant recipients, among whom mortality is exceptionally high. Studies have shown that neither ganciclovir nor CMV globulin used alone is effective.[13] Any commercially available globulin, used in sufficiently high volume, can be combined with ganciclovir. The advantage of the hyperimmune globulin, of course, is the smaller volume required for efficacious treatment.

MONOCLONAL ANTIBODIES

Among those working with monoclonal antibodies, broad-spectrum treatment of gram-negative sepsis using a variety of antiendotoxin antibodies is generating the most interest. In the United States alone, gram-negative bacteremia accounts for 100,000 to 300,000 cases of illness yearly. Septic shock occurs in about a third of cases, with a mortality rate of 40% to 50%; the mortality without shock is 10% to 15%. Antibiotic therapy alone is not achieving the desired outcome and has created the need for alternative treatment, such as monoclonal antiendotoxin antibody.

Future monoclonal antibody research will increasingly consider the anti-mediator concept. This theory moves beyond that of bacteria attacking the host and involves a mediator, such as tumor necrosis factor (TNF). TNF is emerging as the predominant mediator of sepsis and septic shock. Studies[14,15] that correlate TNF levels in the serum of septic patients with the outcome are reported frequently in the literature and clearly point to an association. But many questions remain unanswered. For example, is TNF the only important mediator? Must TNF antibody be given prior to infection, or can it intervene after infection and sepsis occur? Clinical trials of neutralizing TNF monoclonal antibody are underway. If TNF antibody is well tolerated, a multicenter trial to assess the its role in septic syndrome patients will undoubtedly be undertaken within the year.

REFERENCES

1. Shackleford PG, Polmar SH, Mayus JL, Johnson WL, Corry JM, Nahm MH. Spectrum of IgG2 subclass deficiency in children with recurrent infections: prospective study. J Pediatr 1986; **108(1):**647–653.
2. Silk H, Geha RS. Intravenous gammaglobulin (IVGG) prophylaxis in children with IgG2 deficiency. J Allergy Clin Immunol 1987; **79:**188.
3. Chirico G, Rondini G, Plebani A, Chiara A, Massa M, Ugazio AG. Intravenous gammaglobulin therapy for prophylaxis of infection in high-risk neonates. J Pediatr 1987; **110:**437–442.
4. Cooperative Group for the Study of Immunoglobulin in Chronic Lymphocytic Leukemia. N Engl J Med 1988; **319:**902–907.
5. Winston DJ, Pollard RB, Winston G Ho, et al. Cytomegalovirus immune plasma in bone marrow transplant recipients. Ann Intern Med 1982; **97:**11–18.
6. Bowden RA, Sayers M, Flournoy N, et al. Cytomegalovirus immune globulin and seronegative blood products to prevent primary cytomegalovirus infection after marrow transplantation. N Engl J Med 1986; **314:**1006–1010.
7. Sullivan KM, Kopecky KJ, Jocom J, et al. Immunomodulatory and antimicrobial efficacy of intravenous immunoglobulin in bone marrow transplantation. N Engl J Med 1990; **323:**705–712.
8. Krasinski K, Borkowsky W, Bonk S, Lawrence R, Chandwani, S. Bacterial infections in human immunodeficiency virus-infected children. Pediatr Infect Dis J 1988; **7:**323–328.
9. Hague RA, Yap PL, Mok JYQ, et al. Intravenous immunoglobulin in HIV infection: evidence for the efficacy of treatment. Arch Dis Child 1989; **64:**1146–1150.
10. Jackson GG, Perkins JT, Rubenis M, et al. Passive immunoneutralisation of human immunodeficiency virus in patients with advanced AIDS. Lancet 1988; **2(Sep):**647–652.
11. Karpas A, Hill F, Youle M, et al. Effects of passive immunization in patients with the acquired immunodeficiency syndrome-related complex and acquired immunodeficiency syndrome. Proc Natl Acad Sci USA 1988; **85:**9234–9237.
12. Pennington JE, Pier GB, Small GJ. Efficacy of Intravenous Immune Globulin for Treatment of Experimental Pseudomonas Aeruginosa Pneumonia. Journal of Critical Care 1986; **1:**4–10.
13. Reed EC, Bowden RA, Dandliker PS, Lilleby KE, Meyers JD. Treatment of cytomegalovirus pneumonia with ganciclovir and intravenous cytomegalovirus immunoglobulin in patients with bone marrow transplants. Ann Intern Med 1988; **109:**783–788.
14. Girardin E, Grau GE, Dayer J-M, Roux-Lombard P, J5 Study Group, Lamber P-H. Tumor necrosis factor and interleukin-1 in the serum of children with severe infectious purpura. N Engl J Med 1988; **319:**397–400.
15. Waage A, Halstensen A, Espevik T. Association between TNF in serum and fatal outcome in patients with meningococcal disease. Lancet 1987; **1:**355–357.