Long Term Maintenance of Immunity in Patients with Common Variable Immune Deficiency by Plasma Transfusion*

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ABSTRACT

The AIDS crisis and the fear of blood product contamination stimulated the development of a designated plasma collection and transfusion for patients with common variable immune deficiency.

Four patients have been maintained over 1 year; 5 years and 10 months; 8 years and 7 months; and 12 years. A new crisis affecting commercial IgG manufacturing, owing to recalls, has made the life saving product scarce, threatening patients' health maintenance.

Our experience over a long time has demonstrated that plasma transfusion is equivalent to management with commercial IgG. The program of product collection and patient management includes testing the collected plasma for IgG content, selecting ABO compatible plasma, and following patients with IgG trough levels, prior to each transfusion, to assure sufficient immune globulin administration.

Introduction and Discussion

Serum protein analysis by paper electrophoresis in 1952 was the basis for the discovery by Bruton1 of agammaglobulinemia in pediatric patients. Advances in clinical chemistry measuring immunoglobulin (IG) by nephelometry,2 employing highly reactive antibodies to the IG, permit dependable assessment of normal values for IgA, IgG and its subclasses, and IgM, thus defining IG levels sufficient to maintain an infection free life for the individual (table I). In patients with common variable immune deficiency (CVID), indications for treatment are frequent respiratory infections, sinusitis, and lung function deterioration.3 If the gastro-intestinal tract is affected, gastric atrophy may ensue, or chronic diarrhea with Giardia lamblia may create nutritional problems. Once gamma globulin was demonstrated to help fight infection, therapeutic replacement in IG deficient patients had to be made available.4,5

Plasma fractionation by Cohn6 et al, demonstrating the isolation of IgG from human plasma, gave birth to a large industry of collecting plasma from between 1,000 to 6,000 donors and providing the source pool for fractionation. Intravenous preparations replaced IgG treatment with intramuscular injection, which caused pain, slowed the absorption of the IG, and occasionally caused local proteolysis.7

Intravenous immunoglobulin preparations must contain 90 percent intact IgG, with nor-
TABLE I

Immunoglobulin Concentration
Modified from Clinical Guide to Laboratory Tests
2nd Edition N. Tietz

<table>
<thead>
<tr>
<th></th>
<th>IgA mg/dL</th>
<th>IgG mg/dL</th>
<th>IgM mg/dL</th>
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<tbody>
<tr>
<td>1 mo</td>
<td>2–50</td>
<td>1 mo 250–900</td>
<td>1 mo 20–80</td>
</tr>
<tr>
<td>1 yr</td>
<td>15–110</td>
<td>1 yr 340–1200</td>
<td>1 yr 40–150</td>
</tr>
<tr>
<td>&gt;12 yr</td>
<td>40–350</td>
<td>&gt;6 yr 650–1600</td>
<td>&gt;12 yr 50–300</td>
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IgG Subclasses
Percent of IgG
IgG1 60–70; IgG2 14–20;
IgG3 4–8; IgG4 2–6

mal ratios of subclasses, (IgG1; to IgG4)3 and be negative for viral marker testing (HIV, HTLV, HBV, HCV,). Plasma collected from donors who subsequently have abnormal viral marker test results or are members of a family with Jacob Kreutzfeld disease, resulted in the recall of plasma pools, used in the manufacture of IG, which accounts for the IG shortage currently being experienced by the industry.

Lyophilized intravenous immune globulin preparations are easy to administer, can be stored for use, and do not have to be ABO blood group compatible. Manufacturers’ instructions include caution by using slow administration to avoid reactions.

Single donor plasma, by apheresis with the Autoperesis-C,* not salvaged plasma after whole blood collection, provides a component that contains IgG and its subclasses, as well as IgA and IgM, the immune globulins present in the donors plasma. Fractionation usually leaves little IgM or IgA; both are providing important functions for maintaining immunity in the patient. This difference in products provided the encouragement to use a single donor plasma for immune globulin replacement at Central Kentucky Blood Center.

There is no clear definition on IG levels known to protect the individual from the infections commonly encountered that need to be prevented in these immune deficient patients. It is suspected that functional levels may be considerably lower than in the normal individual. Cunningham-Rundels7 and Shiff et al8 demonstrated that it is important to determine the pre-treatment blood level (through level) since the levels right after transfusion vary widely. Trough levels reflect, obviously, the lowest point prior to infusion of immune globulins and are the result of 30 days of decay and utilization during this period. After the initial saturation stage, a fairly stable level occurs after 26 to 86 days. This is achieved individually by each patient depending on metabolism and IG utilization. Normal individuals are reported to have a 21 day half-life for IG. Adequate through levels are between 100 and 200 mg/dl.

Patients receiving replacement therapy must be monitored for absence of infection, which is the best indicator to document therapeutic efficacy. The special NIH Consensus Conference in 1990 on Intravenous Immunglobulin, for prevention and treatment, encouraged research on specific antibodies. As this study demonstrates, the long term outcome measures clearly demonstrate that patients free of infectious diseases are the result of effective replacement therapy.

Continuous flow, using the Plasmacell-C membrane separation to collect plasma from donors under sterile conditions, alternates plasma collection and red cell reinfusion. The volume of plasma collection is dependent on the donors’ hematocrit and weight. As example, with a 52 percent hematocrit and a weight >175 lbs, the plasma collection would be 520 ml. The same donor with an HCT of 41 percent would permit the collection of 630 ml. If the donor’s weight is <175 lbs, the plasma collection could be 755 ml. Since 300 ml of plasma contains sufficient amounts of IG, each donor can provide 2 units for treatment with one donation for the adult patient (table II). All donors must meet the blood donor qualification and the extensive viral testing that is performed on every donation. All donors are volunteers and in this program are designated for the patient

* Baxter Health Care Corporation, Deerfield IL 60015.
TABLE II
Plasma Collection by Apheresis for One Year 1997

<table>
<thead>
<tr>
<th>Median collection</th>
<th>830 ml; range 620 – 1350 ml.</th>
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<tr>
<td>Final unit for transfusion</td>
<td>310 – 675 ml.</td>
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<tr>
<td>IgG / unit average</td>
<td>8.94 g range 4.1 – 10.5 g.</td>
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<table>
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<th>Patient’s trough levels during 1997</th>
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<tbody>
<tr>
<td>Average</td>
</tr>
<tr>
<td>Range from</td>
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because of the requirement of ABO compatibility and sufficient IG content in the collected plasma. The standard operating procedure clearly defines these donors, since their special mission is IG replacement and their plasma is ABO compatible with the specific recipient. The other advantage of this select donor population is the greater frequency to donate, with each donation undergoing repeated important viral testing. These donors all have tested negative during the years they have been part of the project.

For recipients with an antibody to IgA, IgA deficient plasma is made available. The recipient with IgA, even in small amounts, usually does not develop the anti-IgA antibody. But severe IgG deficiency frequently leads to the development of the anti-IgA antibody. In such patients, even small amounts of IgA may provoke a severe anaphylactic reaction if IgA is transfused. Just 0.01 ml of the donor’s serum, collected under sterile conditions, will provide the testing material for the intradermal skin test. A positive reaction will result, characterized by an immediate raised induration of greater than 1 cm, if the patient has developed an antibody. One patient reacted after 3 plasma transfusions from his sister and had to be transfused with IgA deficient plasma for more than 5 years. During this time, the patient did not require any treatment with antibiotics for infections, as had been needed prior to his transfusion therapy. Unfortunately, the patient developed a complication, seen in CVI associated with gastric atrophy, which was followed by gastric carcinoma.

Prior to the availability of viral testing for hepatitis C (HCV), this virus was transmitted by IV IG. A study of 77 patients transfused with IV IG in Sweden and New York revealed 21 percent having contracted nonA-nonB hepatitis, most likely today identified as HCV. Since all our donors were tested for alanine amino transferase levels, the normal levels requirement may have prevented HCV contamination prior to HCV testing.

Management of this therapy may appear difficult, but it has been consistent and beneficial to the 4 patients treated over a long time. No institution will be overwhelmed, since the incidence of patients requiring therapy is very low. Reported in Sweden ranging from 14–26–50/ live birth of 10,6 and Australia 24–89; 10.6 Because of the rarity, most publications concern only case reports. Orphan diseases are burdensome for the patient, as it is now apparent that availability of IG therapy is threatened unless it is made available in a competent and safe manner.

Summary

It is not difficult to provide safe and effective therapy to patients with immune deficiency disease. This report demonstrates that over the years it has been possible to provide sufficient immune globulins by plasma transfusion.

References


