

Hyperimmune Globulins

Intravenous immunoglobulin (IVIG) derived from human plasma is the current economic driver for commercial plasma fractionation (1). Approved indications for IVIG include use in primary immune deficiency, secondary immune deficiency, and infection in bone marrow transplantation (2-5). However, the major use is for a variety of "off-label" indications in the broad area of immunomodulation(5). The focus of this short note is directed toward the use of IVIG in infectious disease and, more specifically, the use of hyperimmune globulins. Hyperimmune globulins are immunoglobulin preparations which are enriched in content with a specific immunoglobulin fraction directed against a specific target pathogen.

Current hyperimmune globulin products are successors to convalescent serum.⁶ The history and development of hyperimmune globulin products to 1995 has been reviewed by Landsperger and Lundblad.⁷ In the case of H1N1 virus, the use of plasma (convalescent plasma) obtained from the pandemic sites permitted the manufacture of a hyperimmune globulin.⁸⁻¹⁰ Subsequent work from other investigators has emphasized the utility of convalescent plasma in avian influenza (11) and emphasizes that there is a narrow therapeutic window for intervention (12).

I see four factors which support the increased development of hyperimmune globulin therapeutic products:

- Increasing issues of antibiotic resistance and emerging pathogens.
- A minor component(s) in a commercial IVIG preparation is responsible for the observed clinical effect (13-16). The use of a more specific product would permit a therapeutic effect to be delivered with less protein load and likely reduced adverse reactions.
- Polyclonality of product is an essential, attribute required for effective passive immunization (17). This latter paper raised the potential of recombinant polyclonal antibodies (18).

- Donor plasma undergoes considerable screening for pathogens at the site of collection (19). Additional screening for specific IgG fractions could be easily accomplished with microarray technology. Donor units which have high antibody level could be indentified and collected from the units delivered to the fractionation site.
- Convalescent plasma/serum (9,10, 20) and/or plasma from vaccinated individuals (21-23) can provide starting material for manufacture into therapeutic hyperimmune product. HIV hyperimmune globulin was prepared from an donor population which was HIV seropositive but asymptomatic (24-26).

There is no question that convalescent serum/plasma has been an effective therapeutic modality to treat infectious disease for almost 100 years(6,27) and hyperimmune globulins have been very useful in the treatment of viral diseases (28-30). It is noted that hepatitis B plasma has been shown to be effective and is less expensive that the hepatitis B hyperimmune globulin (31). Since the product attribute which would distinguish a hyperimmune globulin from a normal hyperimmune globulin is target specificity, the key process attribute is the presence of that specific immunoglobulin in the starting plasma. Thus, it should be possible to develop and validate a "generic process" for manufacturing hyperimmune globulin product

The classical approach to the manufacture of hyperimmune products is based on quality attributes of starting plasma. Screening donor plasma either before donation or by selection in sorting prior to fraction can provide plasma with high titers of antibody against the therapeutic target. Selection of donors was used for the preparation of CMV hyperimmune globulin (32-34). Assay method can influence therapeutic effectiveness (35,36). Screening programs have also been used for tetanus (37) and hepatitis B (38).

There are, however, at least two other approaches to a hyperimmune product. It is, however, likely that both are expensive and difficult to validate. Both approaches are based on the development of

monoclonal antibodies against the target pathogens. The first has been mentioned above and involves using a combination of monoclonal antibodies to obtain a synergistic effect (39-42). A related approach is based on the addition of monoclonal antibodies to a polyclonal immunoglobulin (IVIG or hyperimmune globulin) where synergism is obtained (43-47). Bar-Dayana (48) and coworkers compared Pentaglobin® with Sandoglobulin® in binding autoantibodies and suggested that an immune globulin product, Pentaglobin®, which contained substantial amounts of IgM and IgA might be useful in the treatment of autoimmune disease. Subsequent work has supported the value of IgM in an IVIG preparation (49). There is significant work in Russia on the use of antistaphylococcal hyperimmune globulin for antibiotic *Staphylococcus aureus* which was reviewed by Kelly in 2000 (50).

One disadvantage of monoclonal antibodies is that they are static as compared to polyclonal antibodies where composition is continuing changing in response to changes in quality of immunogen stimulation. An example is provided by sequence variation within Botulinum neurotoxin serotypes which binding and neutralization by monoclonal antibodies (51). Dubois and coworkers (52) discuss the issue of antigenic specificity as a potential problem when there is random mutations in viruses. Dubois and coworkers (52) also emphasize the need for early intervention with antibody therapeutics for optimal clinical efficacy. There also has been a problem with glycosylation causes adverse reactions but not with infectious disease (53). A naturally occurring polyclonal antibody population is dynamic reflecting changing pathogen challenges. Passive immunization defined as the transfer a polyclonal antibody population either as convalescent serum or a purified hyperimmune globulin preparation. There is an increased interest in the use of passive immunity via administration of immunoglobulin(6,54-57).

In addition to the approaches to hyperimmune globulin discussed above, it should be possible to purified specific antibody from an IVIG preparation by an affinity process; alternatively a Cohn II +III fraction could be used as well. The caveat to this is that I am not sure whether the cast of supporting

actors in a commercial IVIG preparation are important to the function of the specific antibodies. So, this approach, although attractive from the perspective of a protein chemist, may not be useful. What is possible with current technology is the development of a "fractionation plant" on wheels which could be move to the initial point of a developing pandemic to process convalescent plasma.

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