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IMMUNOGLOBULIN THERAPY IN KAWASAKI SYNDROME AND RSV PROPHYLAXIS

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1. ABSTRACT

Kawasaki syndrome and RSV infection are common illnesses that afflict infants and young children. Recent studies demonstrate that intravenous immunoglobulin (IVIG) treatment significantly reduces the clinical severity of these illnesses. The purpose of the current review will be initially to examine mechanisms of disease pathogenesis in KS and RSV infection. This will be followed by a discussion of the potential mechanisms by which IVIG acts in these two illnesses. In both KS and RSV prophylaxis, an important action by which IVIG may work is primarily through toxin or microbial neutralization resulting in the dampening or prevention of the inflammatory response. Other immunomodulatory actions of IVIG are likely to be operative in these diseases and will be an active area of future research.

2. INTRODUCTION

Since the end of the 19th century, immune serum has been used in the treatment of a number of toxin mediated infectious diseases including diphtheria, scarlet fever, botulism, pertussis, gas gangrene and tetanus. In addition to inactivation of specific toxins, gamma globulins are also used to enhance biologic function against various microbes by complement mediated lysis, opsonization or neutralization. More recently, immunomodulatory functions of intravenous preparations of immunoglobulins (IVIG) have been described which include alterations in cytokine production (1), modulation of T cell function *in vitro* and *in vivo* (2,3), inhibition of antibody secretion *in vitro* (4), increase in natural killer cell activity (5) and increase in antibody-dependent cell cytotoxicity (5). A recently established activity of IVIG is neutralization of staphylococcal superantigen activity (6). In this report, we will review the potential mechanisms of action of IVIG in the treatment of Kawasaki Syndrome (KS) and the experience with IVIG in the prophylaxis of RSV infections. KS represents a vasculitis which may respond to gamma globulin therapy via the neutralization of bacterial toxin(s). Although other mechanisms are likely to be demonstrated as well in both settings, IVIG prophylaxis against RSV infection appears to work primarily through viral neutralization.

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3. Role of IVIG in Kawasaki Syndrome

KS is an acute vasculitis of infancy and early childhood first described by Tomasaku Kawasaki in 1967 (7). This vasculitis can involve all small and medium arteries throughout the body but particularly targets the coronary arteries (8). The clinical features associated with KS are listed in Table I (9). Features of this disease are similar to those found in certain diseases which are recognized to be caused by toxin-producing bacteria, such as toxic shock syndrome and scarlet fever. Untreated KS is generally a self-limited illness lasting 2 to 3 weeks. Coronary artery involvement occurs in 20 to 25% of patients who do not receive therapy within 10 days following the onset of fever (10). Studies in Japan and the United States demonstrated that IVIG plus aspirin given within the first 10 days of onset of fever reduce the prevalence of coronary artery abnormalities to less than 5% (11, 12). Early studies evaluated IVIG at a dose of 400 mg/kg given on 4 consecutive days (10). A subsequent multicentered study demonstrated that a single dose of IVIG, 2 gm/kg, with aspirin was more protective against formation of coronary artery aneurysms (12). In addition to reducing coronary artery disease, high dose IVIG therapy results in a more rapid normalization of laboratory values

Table 1. Diagnostic Features of Kawasaki Syndrome

1. Fever
2. Non exudative, bilateral conjunctivitis
3. Changes in the oral cavity, including:
   - strawberry tongue
   - erythematous
   - fissured lips
   - hyperemic pharynx
4. Changes in the peripheral extremities:
   - induration and erythema of hands and feet
   - periungual desquamation
5. Polymorphous rash
6. Cervical lymphadenopathy
   - (at least one node > 1.5cm diameter)

(albumin, α-antitrypsin, C-reactive protein) as well as more rapid resolution of clinical symptoms (12).

It was also noted that a lower peak IgG level was associated with a worse clinical outcome, suggesting that a therapeutic threshold was necessary to achieve benefit (12). The duration of fever and the degree of inflammation as measured by laboratory tests such as the erythrocyte sedimentation rate was inversely related to the peak IgG level. Even more importantly, the peak serum IgG level following IVIG therapy was significantly lower in those children who developed coronary artery disease. A recent meta-analysis evaluated the efficacy of aspirin and IVIG in the prevention of coronary artery abnormalities (13). The authors concluded that, while both high-dose and low-dose aspirin therapy were associated with a similar risk of coronary artery disease, IVIG at a dose of >1.0 gm/kg was associated with a lower risk of coronary artery involvement than lower doses of IVIG. During a 3 day observation, a single high dose IVIG of 2 gm/kg resulted in a lower incidence of coronary artery disease than when multiple doses of 400 mg/kg IVIG were received. These data suggest that a specific serum IgG concentration must be achieved before inflammation is arrested.

The mechanism(s) accounting for the efficacy of IVIG in the treatment of KS is unknown. However, it is widely agreed that this illness has an infectious etiology. This observation is based on both epidemiologic and clinical findings. In Japan as well as the United States there is an endemic incidence of disease on which epidemics and even pandemics may be superimposed (14). One well documented outbreak in Japan which occurred between November 1985 and May 1986, started around Tokyo, extended to North and South and ultimately involved most of Japan (15). This epidemiologic pattern of spread strongly suggests that the disease is due to an infectious microorganism that may be readily transmitted among young children. Seasonal peaks of KS tend to occur in late winter and spring (14). The peak incidence of KS occurs between 12 and 24 months of age, with over 80% of cases occurring before 5 years of age (14). This disease rarely occurs in adolescents or in children less than 6 months of age. This age distribution is typical of other infectious diseases such as paralytic polio in the pre-vaccine era and varicella in unvaccinated children. It is possible that early in the first year of life, children lose protective maternal antibody, and gradually acquire an immunity during childhood so that by adolescence the disease becomes uncommon.

Extensive serologic and microbiologic studies have failed to identify a consistent microbial agent associated with cases of KS (14). However, studies of the immune response in patients with KS reveal an unusual degree of stimulation (16, 17). The acute stage of KS is associated with increased numbers of activated helper T cells and reduced numbers of suppressor T cells (18-20). A marked polyclonal B cell activation present during the acute phase is reduced by treatment with IVIG (18, 19). Cytokine levels including levels of IL-1, TNF-α, IFN-γ and IL-6 are elevated during the acute phase of the disease and return to normal during convalescence (21-26). Circulating antibodies that appear during the acute stage are cytotoxic to cytokine-stimulated vascular endothelial cells (27, 28). Furthermore, tissue from a fatal case of KS demonstrated endothelial cell activation with the expression of cytokine-inducible molecules such as HLA-DR antigens (29). A mononuclear cell infiltrate consisting of activated CD4 and CD8 T cells as well as monocytes was also seen.

IVIG therapy results in a reduction of the acute symptoms as well as normalization of many of the immunologic aberrations seen in acute KS. Specifically, aspirin and IVIG therapy is associated with an increase in the number of circulating CD8+ T cells, a reduction in the number of activated helper T cells and a reduction in the number of B cells. Several theories have been proposed to explain these immunologic effects by IVIG (Table II). It is likely that IVIG modifies the inflammatory response through more than one mechanism. For example, several reports suggest that IVIG production acts directly on cytokine gene expression via transcriptional and post-transcriptional modulation (30). This suggests that IVIG may downregulate the immune response by a nonspecific immuno-modulatory mechanism. In addition, IVIG may neutralize a causative toxin that results in the massive immune stimulation associated with KS (6).

Staphylococcal enterotoxins and strepto-coccal pyrogenic exotoxins (SPE) B and C have the ability to activate B cells, T cells and macrophages (reviewed in references 31 and 32). These bacterial products have been defined as superantigens. Such toxins bind to the class II MHC proteins on the surface of the antigen presenting cells and stimulate T cells which express particular Vβ gene segments.

Table 2. Possible Mechanisms of IVIG Action in Kawasaki Syndrome

1.Anti-idotypic modulation of anti-endothelial antibodies.
2. Inhibition of cytokine-induced endothelial activation.
3. Reduction of cytokine production.
4. Anti-toxin specific antibodies which neutralize the causative superantigen.

Similarly, superantigens are potent stimulators of IL-1 and TNF-α production by macrophages (33). Patients with toxic shock syndrome, a prototypic example of disease caused by a superantigen (TSST-1), have a dramatic expansion of Vβ2+ T cells (34).

To determine whether the immune activation associated with acute KS represents a response to superantigen(s), studies were conducted on the T cell repertoire of patients in the acute phase of KS (35, 36). Peripheral blood mononuclear cells from 19 patients with acute KS were analyzed for T cell receptor Vβ gene expression using two methods: semiquantitative polymerase chain reaction analysis and flow cytometry. Patients with KS demonstrated elevated levels of Vβ2 and Vβ8.1 T cells in comparison to cells from control patients with other febrile illnesses which showed no changes (35). During convalescence, the proportion of Vβ2 and Vβ8.1 T cells returned to normal levels. Other Vβ T cell populations were analyzed and comparisons were made between acute and convalescent specimens of patients with KS from Japan as well as two sites in the United States. None of the other Vβ populations were found to be elevated. These results are consistent with the hypothesis that the immune stimulation of KS is triggered by a bacterial toxin with superantigenic activity. This selective expansion of circulating Vβ2 T cells is similar to the changes in peripheral blood lymphocytes described in toxic shock syndrome, an illness that shares many clinical manifestations of KS (35). Such a marked expansion of T cells expressing a specific Vβ rarely occurs in response to a conventional antigen. A second study using a Vβ2 specific monoclonal antibody confirmed the increased expression of Vβ2 and to a lesser degree of Vβ8.1 in peripheral blood T cells of 13 patients with acute KS (36).

Following our report in 1992, several other groups examined the TCR repertoire during the acute stage of KS. A report by Pietra *et al*.. did not detect an increase in any particular Vβ family (37). However, one patient with acute KS demonstrated elevated Vβ2 T cells and two patients demonstrated a decrease in Vβ2 T cells. During convalescence, these changes reverted to normal consistent with a superantigen effect in these patients. In this regard, superantigens are capable of causing either elevations or reductions in circulating T cells bearing specific TCR Vβ's. A report by Sakaguchi *et al.* also failed to detect expansion of CD4 and T cells bearing Vβ2 or Vβ8 receptors among Japanese children with acute KS (38). The authors suggested that superantigens initiating the immunopathology of KS in various geographic locations may be different (38).

An alternative explanation is that the ability to detect expansion of Vβ-specific T cells is dependent on the time interval after onset of illness. Indeed a recent study by Curtis *et al.* (39) did confirm increased Vβ2+ T cells in acute disease. However, significantly elevated percentages of Vβ2+ T cells were detected only during the second week of illness. During the first week and after the second week of acute KS, T cells did not demonstrate Vβ skewing. After the second week of illness, stimulated T cells may have already migrated to tissues and therefore may no longer be detectable in the peripheral blood. Therefore, the reason that some investigators have had difficulty in demonstrating T cell abnormalities may be attributed to the timing of collections of the blood specimen.

In a recent report by Leung *et al.*, myocardial tissue and coronary artery tissue were studied from a patient who died of acute KS (40). Immunohistochemical examination of the mononuclear cell infiltrate of frozen tissue sections from the myocardium and the right coronary artery as compared to spleen demonstrated enhanced Vβ2 expression in the coronary artery, particularly in the myocardium. Sequence analysis of the Vβ2 chain genes from T cells isolated from the myocardium demonstrated extensive junctional region diversity. While the response to stimulation by most conventional antigens results in cells with limited junctional diversity of the T cell receptor, extensive junctional diversity is a typical response to a superantigen.

In a separate study, Yamashiro and his colleagues reported a selective expansion of Vβ2+ T cells in the small intestinal mucosa of patients with acute KS but not in the control subjects (41). Based on these observations, they suggested that the GI tract may be the primary site of entry for a superantigen-secreting organism causing acute KS. Indeed, preliminary data from their group also indicates that staphylococci and streptococci can be isolated from small intestinal fluid of KS patients.

Considering that three independent groups of investigators have found evidence of increased numbers of Vβ2+ T cells in acute KS, the next important hurdle was identification of the putative superantigen(s). To determine the potential superantigen(s) involved in this Vβ2+ T cell

expansion, Leung *et al.* carried out the following study (41): Samples from sixteen consecutive patients with KS were cultured for the presence of superantigen producing gram-positive bacteria. Skin (groin, axilla) and mucous membrane (rectum, throat) cultures were obtained from 16 patients who satisfied established criteria for KS before IVIG therapy was administered. Fifteen control patients with fever and rash served as control. All group A β hemolytic streptococci and all coagulase positive *S. aureus* isolates were screened for toxin production. Cultures from patients with KS and control patients were screened in blinded fashion. Bacteria producing superantigens were found in 13 of 16 KS patients, but they were present in only 1 of 15 control patients ($p<.0001$). Eleven of 13 toxin positive cultures from patients with KS were due to TSST elaborating *S. aureus* and 2 of 13 were due to *streptococci* producing SPEB and SPEC. TSST-1 and SPEC are known to possess superantigenic activity which stimulate expansion of Vβ2+ T cells.

Twelve of the 13 culture positive patients had toxin producing *S. aureus* isolated from the mucous membranes of the upper or lower gastrointestinal tract. Only 1 of 13 patients had toxin producing bacteria on the skin and none showed bacteria colonizing the mucous membranes. This is consistent with the observation of Yamashiro *et al.* (41) of marked Vβ2+ T cell expansion in the gastrointestinal tract of patients with acute KS.

Since this report in 1993, TSST secreting *S. aureus* have been isolated from a number of patients with KS from different regions of the United States. These include KS patients with coronary artery disease (Schlievert and Leung, unpublished observations). However, one group has been unsuccessful at detecting this organism from patients with KS (43). The inability to recover this organism may be due to the relatively low concentration of this toxin producing *Staphylococcus* on the surface of mucous membranes. To reliably identify toxin producing strains, we have found it necessary to meticulously study numerous colonies from each culture. The failure to find seroconversion to TSST-1 has been used as evidence against a role for this toxin in KS (43). However, this approach is flawed because seroconversion rarely ever occurs following the acute phase of other superantigen-mediated diseases such as staphylococcal TSS. Furthermore, all such KS patients were treated with high dose IVIG which is known to inhibit antibody synthesis.

Takei *et al.* (6) has demonstrated that IVIG contains high concentrations of neutralizing antibodies which inhibit the T cell response to eight different staphylococcal superantigens. Using affinity absorption techniques, it was shown that this T cell inhibitory effect was mediated by anti-toxin specific antibodies in IVIG. Clinical and subclinical infections with *S. aureus* presumably result in production of antibodies to staphylococcal toxins with increasing age. Pooled IVIG which is obtained from several thousand donors can be expected to contain variable titers of antibodies to staphylococcal toxins. Thus, it is possible that the beneficial effect of IVIG in KS is, in large part, due to the presence of antibody which inhibits bacterial toxin-induced stimulation of the immune response.

As noted earlier, there appears to be a threshold IgG level which is necessary to reduce the prevalence of coronary artery disease in patients with KS. In fact, certain patients require more than one dose of IVIG before demonstrating a beneficial effect (44). In an earlier report, we demonstrated considerable variation between four different IVIG preparations in their ability to inhibit superantigenic activity due to TSST-1 (45). We propose that certain patients who fail to satisfactorily respond to IVIG may not have attained a sufficient titer of antibodies to bacterial toxins. In these situations, sequential doses may be necessary to achieve a protective titer. We have also provided evidence that children who develop KS lack immunity to TSST-1 at the time of presentation, while convalescent specimens contain passively acquired activity against TSST-1 derived from IVIG therapy (45). We believe that acquisition of this activity is responsible for the resolution of symptoms.

In Figure 1, a possible sequence of events in the pathogenesis of KS is proposed: a susceptible host becomes colonized on the mucous membranes by a superantigen-producing organism, most often a coagulase-positive *S. aureus*, although other toxin producing bacteria may be involved. In a host who lacks antibodies to toxin, the toxin is absorbed resulting in selective stimulation of Vβ2+ T cells. A cascade of immune stimulation follows, with an increase in the number of activated helper T cells, B cells and macrophage/monocytes. Macrophage stimulation results in an elevated levels of cytokines. The elevated cytokine levels induces fever and the clinical findings of KS as well as the increased levels of acute phase reactants. Increased cytokine levels also results in the expression of new antigens on the surface of endothelial cells, making the cells susceptible to cytotoxic antibodies, more thrombogenic and more susceptible to attack by leukocytes. Selective infiltration of Vβ2 T cells into the coronary arteries and the myocardium leads to vascular injury and myocarditis and results in formation of aneurysms. The unusually severe irritability in patients with KS may be a direct neurotoxic effect of the bacterial toxin.

It should be noted, however, that the lack of anti-toxin antibodies as a risk factor for superantigen-mediated diseases has only been shown for Toxic Shock Syndrome. Indeed, in patients with atopic

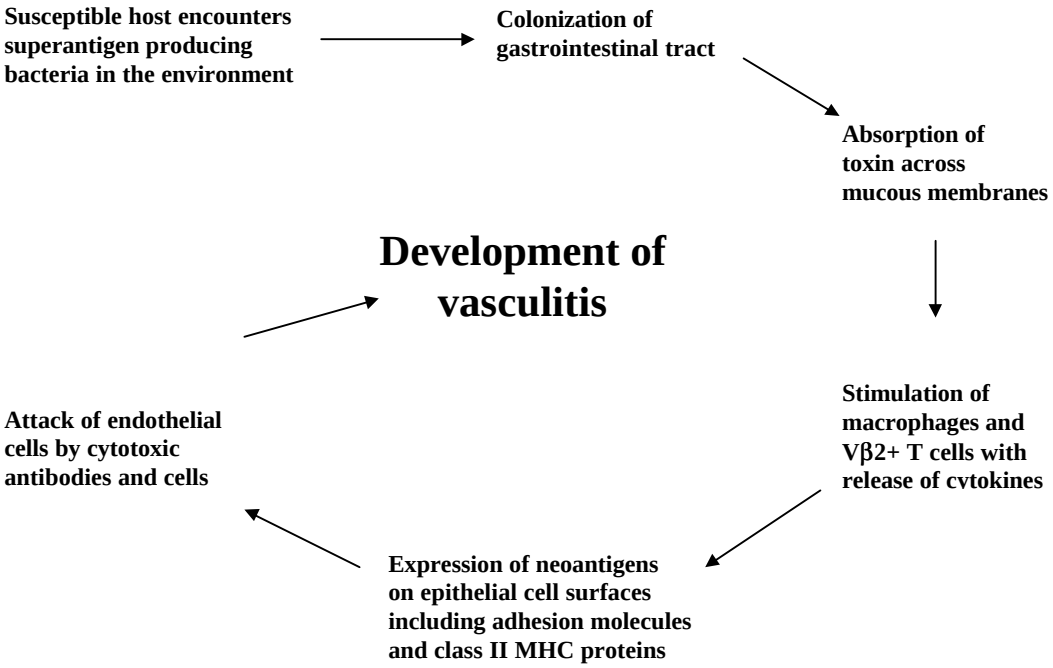

Figure 1. Postulated scenario for pathogenesis of Kawasaki Syndrome.

dermatitis, who are chronically colonized with high numbers of superantigen producing staphylococci, we have found high serum IgG titers to staphylococcal toxins. Nevertheless, application of toxins or superantigens to their skin results in an inflammatory skin lesion indicating that circulating anti-toxins do not prevent onset of local inflammation in response to superantigens. Thus, aside from toxin neutralization, the administration of IVIG in acute KS is likely to have a number of different immunomodulatory effects that leads to reduced inflammation.

4. RSV prophylaxis and the role of passive immunity

Respiratory syncytial virus (RSV) was first isolated in 1956 (45). The significance of this virus as a cause of clinical disease was first reported by Chanock in 1961 (46). By the early 1970s, RSV was recognized to be an important cause of nosocomial disease among children. It is now recognized that RSV is the single most important respiratory pathogen in infancy and early childhood (47). Predictable yearly outbreaks of RSV disease begin in late fall or early winter and continue into the spring months. Nearly 30% of primary RSV infections result in lower respiratory tract disease consisting of bronchiolitis and pneumonia. Serologic surveys indicate that most children are infected by RSV before 2 years of age. Despite such widespread immunity, reinfection by RSV is common in both children and adults. Forty to 50% of children hospitalized with bronchiolitis and 25% of pediatric hospitalizations due to pneumonia are caused by RSV (47). Children with certain underlying conditions are particularly at risk of severe disease and hospital-ization. This includes low birth weight infants, children with chronic lung disease such as bronchopulmonary dysplasia, children with congenital heart disease and children with immunodeficiencies (48-51).

Epidemiologic studies have found that term neonates tend to experience less severe RSV disease in the first few weeks of life when maternal neutralizing antibodies are highest (51, 52). Studies in both term and premature infants have demonstrated an inverse relationship between severity of RSV illness and the level of maternal neutralizing antibody. Severe RSV-mediated lower respiratory tract disease in infants tends to occur when the concentration of antibodies fall to low levels. These observations suggest that serum neutralizing antibodies to RSV play a beneficial role in preventing the lower respiratory tract disease caused by RSV.

Active immunization against RSV has proceeded cautiously because of concern that augmentation of the immune response may result in

worsening pulmonary complications in RSV infected infants (53). In the 1960s, using a formalin inactivated RSV vaccine, the incidence of severe acquired RSV disease proved to be greater in vaccinated infants than in control children (54-56). Serologic studies subsequently demonstrated that although the complement fixation antibody response in the vaccinees was satisfactory, the neutralizing antibody response to RSV was poor. After natural RSV infection, the vaccinees experienced an appropriate neutralizing antibody response, suggesting an incomplete immune response following use of the formalin inactivated vaccine. Since that experience, attempts to develop a safe and immunogenic RSV vaccine have met only with a limited success.

As an alternative to active immunization, the role of passive immunization in the prevention of serious RSV illness has been examined in both animals and humans (57). RSV contains at least 10 viral polypeptides, 2 of which are surface glycoproteins. The G glycoprotein is involved in attachment of the virus to a susceptible host cell. The smaller of the two molecules, the fusion glycoprotein (F), appears to be responsible for viral penetration of the host cell and for fusion of infected cells resulting in cell to cell spread. Neutralizing epitopes have been identified on both glycoproteins. In adults, there is an inverse correlation between antibody levels to F and G glycoproteins and susceptibility to reinfection. In infants, one study found no significant difference between the concentration of antibodies to F and G between infants who became infected and those who did not (58).

Based on animal studies, immunity to RSV is felt to depend largely on antibodies to F and G. Newborn cotton rats experience RSV replication in the upper and lower respiratory tract following intranasal inoculation, although they do not develop illness. In the cotton rat, a high titer of intraperitoneally administered, neutralizing antibody to RSV is protective against disease (59). The titer of virus that can be recovered in the lungs varies inversely with the concentration of neutralizing antibody in the serum. In the animal model, a neutralizing titer of $\geq$1:350 is associated with protection of the lower airway tracts (60). Serologic studies in newborn infants has shown that neutralizing titers between 1:300 and 1:400 results in similar protection from disease.

As a result of these observations, an initial study was begun, in 1988, to examine the safety of a standard, commercial immune globulin. This immune globulin had an RSV neutralizing antibody titer of 1:1100 (61). A controlled trial was conducted between 1989 and 1990 using an IVIG from the same manufacturer (Gamimune N, Cutter Biological, Miles, Inc., Berkeley, CA) to evaluate protection against RSV-induced disease (62). During 2 RSV seasons, a total of 49 children with severe congenital heart disease or bronchopulmonary dysplasia were randomized to receive monthly infusions of IVIG at a dose of 500 mg/kg or to be followed as controls. There were six RSV infections in the prophylaxis group and six RSV infections in the control group. There was a trend toward less severe RSV disease in the IVIG recipients as determined by the length of hospitalization. In contrast to 51 hospital days among 4 RSV infected controls, four of 6 IVIG recipients were hospitalized for a total of 35 days due to RSV illness. The average peak serum RSV neutralizing titer was 1:124 with trough titers of 1:57. Although a significant difference between groups could not be demonstrated, there was a trend toward fewer hospital days in the IVIG recipients. Failure to demonstrate a significant difference between groups was most likely due to an inability to attain a sufficient titer of RSV neutralizing antibody.

These results suggested that an IVIG preparation with a higher titer of RSV neutralizing antibody would be necessary to provide more effective prophylaxis against RSV disease. An RSV hyperimmune globulin was prepared at the Massachusetts Public Health Biologic Laboratories from human plasma selected because of a high titer of neutralizing antibodies to RSV. The RSV neutralizing antibody titer ranged from 1:2400 to 1:8073. Using this product, a randomized, blinded, multi-institutional trial was conducted over three respiratory virus seasons to evaluate efficacy and safety in three groups of high risk children: congenital heart disease, bronchopulmonary dysplasia and prematurity (63). Two hundred and forty nine infants and young children received monthly infusions between November and April during three consecutive respiratory virus seasons. Participants were randomized to receive RSVIG at 750 mg/kg, 150 mg/kg or no immune globulin. Infants were seen when symptoms developed and respiratory status was assessed in a blinded fashion. In the high dose group there were fewer RSV lower respiratory tract infections (P=0.01), fewer hospitalizations (P=0.02) and fewer hospital days (P=0.02) than in the control group. In the low dose group, statistical significance was not obtained in any of these parameters. The trough serum titers in the high dose group generally exceeded 1:200. Thus, this trial demonstrated that a hyperimmune RSV globulin which is able to maintain neutralizing serum titers greater than 1:200 reduces both the incidence and severity of RSV illness.

In January 1996, RSVIG was approved by the FDA for immunoprophylaxis of two groups of children known to be at high risk of severe RSV disease. In addition to the study by Groothuis *et al.* (64), supporting data came from 3 additional trials indicating that polyclonal, hyperimmune RSVIG has a role in prevention of disease in carefully selected infants with prematurity who either have or do not have bronchopulmonary dysplasia. The largest trial

included 510 infants who were randomized to either placebo infusions or to 750 mg/kg RSVIG on a monthly basis during the respiratory virus season. Perhaps, the most striking data from that trial indicated that the total days of hospitalization due to any respiratory illness was reduced from 317 days/100 control children to 170 days/100 children who received prophylaxis. This observation suggests that the polyclonal product was useful both in reducing disease severity of RSV as well those due to other respiratory viruses.

This polyclonal immunoglobulin represents a first generation product that is likely to be replaced by alternative approaches to immunoprophylaxis. The disadvantage of hyperimmune RSVIG is that it must be administered intravenously and that a dose must be given every 4 to 5 weeks in order to sustain a sufficiently high titer of neutralizing antibodies to reduce the risk of the disease. Two alternative therapies under investigation include monoclonal IgG and monoclonal IgA antibodies directed against the F protein. The potential advantage of this approach is that a monoclonal antibody can be administered less frequently than once a month and still maintain a protective titer. It is likely that the antibody can be administered by an intramuscular route rather than intravenously and still produce a protective titer. An alternative approach is the use of a IgA monoclonal antibody which could be administered topically to the mucous membranes of the upper respiratory tract. While it is still early to discern the practicality of monoclonal antibody therapy in preventing RSV disease, such therapy presents a promising next step in the control of RSV infections, the most common respiratory pathogen in children.

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