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Rational Use of Immunomodulators in Pediatrics[1]

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Immunomodulators are agents that regulate the immune response. In the past years there have been tremendous researches and studies on various biologic agents used to manipulate immune regulation for the prevention and management of infectious diseases in infants and children. Our task is to review and evaluate some of the immunomodulators that are commonly encountered and to determine their usefulness in the management of childhood illnesses.

The classification of the immunomodulators can be done in several ways. In general they are divided into non-specific and specific types. The non-specific types are more varied and potential uses are towards augmenting immune function in a septicemic or susceptible host, or during relatively immunodeficiency states. Unlike those for the specific type of immunomodulators, some of them are being used for sepsis without a known pathogen; as anti-inflammatory agents or in some cases as anti-viral agents. The specific immunomodulators target infection from particular agents such as when a vaccine is given. Another area of concern would be in the biologic response of any individual to a particular allergenic substance or drug which is the essence of allergen immunotherapy, or sometimes called desensitization.

The tentative list of both non-specific and specific immunomodulators is given here.

NON-SPECIFIC IMMUNOMODULATORS
Immunoglobulins
Corticosteroid
Cytokines
Growth factors
Cytotoxic agents
Immunonutritional
Isoprinosine

Specific immunomudulators include immunization and allergen immunotherapy.

Since each of this topic is a major volume in itself, we will concentrate only on a few topics that I believe may have some practical applications for our pediatricians. Thus I chose to touch on corticosteroids, immunonutritionals, isoprinosine and discuss more lengthily on immunoglobulin especially on the intravenous form as this has captured a lot of attention in recent years.

IMMUNOGLOBULINS

The human serum has varied concentration of different immunoglobulin fraction. The principal immunoglobulin constituent in the serum of a healthy adult is IgG (75-80%) whereas IgM (approximately 10%) and IgA (approximately 5%) are present in relatively small quantities. Within the immunoglobulin classes, identifiable subgroups exist and are known as subclasses. There are 4 IgG and 2 IgA classes.

The immunoglobulin fraction of human serum contains antibodies against the different causative agents of infection. The distribution of antibody activity varies among the individual immunoglobulin classes or subclasses. Immunoglobulin products from human serum are being used increasingly in the prophylaxis and therapy of viral and bacterial infections and for substitution therapy in the antibody deficiency syndromes. In addition they are used in a variety of autoimmune diseases.

The immunoglobulin products consist mainly of IgG with a small amount of IgA. IgM is generally present in trace amounts only. IgG is of foremost importance because it is the antibody

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against protein antigen, bacterial toxins and viruses. Its main mechanisms of action include virus neutralization, bacterial toxin neutralization, bacteriolysis (cytolysis), opsonization of bacteria and endotoxins and synergy with antibacterial chemotherapy.

The commercially available immunoglobulins are present in two forms, the intramuscular (IG) and intravenous forms (IVIG). The intramuscular form (IG) has been available since the mid 20th century. It has been demonstrated that gammaglobulin administered on a monthly basis on patients with hypogammaglobulinemia decreased the incidence of infection. Thus antibody replacement for immune deficiency was given routinely. Some specific infectious disease where IG is being given commonly are measles and hepatitis.

For antibody immunodeficiency, the dose of IG is 100 mg/kg/dose. It is usually given at monthly intervals but the interval may be reduced if symptoms of infection persist or recur.

IVIG is used primarily for primary and secondary antibody deficiencies and immunoregulatory disorders such as immune thrombocytopenic purpura (ITP) and Kawasaki disease.

Serious adverse effects like anaphylactic reactions are quite rare. These reactions usually manifest as anxiety, nausea, vomiting, malaise, flushing, facial swelling, cyanosis and loss of consciousness. Among the milder side effects, the following are seen: transient tenderness at injection site, cutaneous reactions and fever. The circulatory reactions of tachycardia or bradycardia progressing to shock are rare.

On some occasions, subcutaneous immunoglobulin infusion as an alternative to intramuscular injection has been done. The injections are self-administered into the abdominal wall through the use of a battery operated pump. It enables patients to receive increased quantities of IG and maintain higher serum levels of IgG. This is less expensive than IVIG. The usual dose is 100 mg/kg/week. This route has also been successfully used in immunodeficient patients with poor venous access, aseptic meningitis, or anaphylactic reactions to IVIG.

In specific clinical conditions, after many clinical trials, the use of IG has been proven to be non-beneficial or at most controversial. In asthma and allergy, no significant benefit was shown based on double-blind studies. In acute infections such as ARI-otitis, tonsillitis, skin infections and recurrent fever, no clinical benefit was also seen. In burns, where initial studies showed reduced mortality for severely burned children, subsequent trials negated the results.

In severe bacterial infections, no demonstrable therapeutic benefit was also seen. In prematurity, the use of IG which is theoretically justifiable since prematures are relatively hypogammaglobulinemic, the results of clinical trials showed IG to be of limited and unproven value.

In the past decade, the availability of IVIG captured a lot of interest. IVIG is in the form of treated human immune serum globulin rendered free of complexes and safe for intravenous infusion. It is an important therapeutic modality in immune deficiency and auto immune disease and contains antibodies pooled from a large number of donors.

The indications for its use again center on (1) replacement and prophylactic therapy for primary and secondary immunodeficiency status; (2) management of specific inflammatory and immunologic disorders; and (3) passive immunization for certain high risk patients and in other miscellaneous conditions. IVIG replacement and prophylactic therapy include those with x-linked agamaglobulinemia, HIV infection and AIDS, post-bone marrow transplant, chronic lymphocytic leukemia and other malignancies with antibody deficiencies like multiple myoloma. Specific inflammatory and immunologic disorders where IVIG has been beneficial are immune thrombocytopenic purpura (ITP) and Kawasaki disease.

For passive immunization of high risk patients, the prematures and low birth weight infants have been shown to benefit from IVIG as well as some nephrotic syndrome cases with hypogammaglobulinemia. Other uses of IVIG are in Guillain-Barre Syndrome (GBS), trauma, surgery and burn patients. A very recent issue is its effect on a very important disease in Southeast Asia-Dengue Hemmorhagic Fever.

An unpublished, randomized double-blind controlled trial by Frias *et al* done in the Philippines, enrolled 214 patients 6 months-14 years diagnosed to have DHF gr. III and IV according to WHO classification. They were comparable in age, sex and severity of illness. Mortality and morbidity in the 2 groups, one given IVIG and another a control group were compared. The clinical course of the 214 DHF patients were compared as well as the adverse effects during therapy. It was noted that development of adverse events on IVIG therapy was calculated at a relative risk of 1.6.

Over-all mortality for DHF patients showed a favorable outcome for the IVIG group with a 15% mortality compared to 28% for the control. This was found to be statistically significant. Another study by Calma in 1993 showed that in 11 DSS patients given IVIG, there was no mortality.

The possible role of IVIG in DHF/DSS are summarized into the following mechanisms: (1) blockade of immunologic activation; (2) blockade of the inflammatory response directed to vascular surfaces; (3) saturation of Fc receptors on platelets and reticuloendothelial cells; and (4) provision of a specific neutralizing antibodies to counteract the infectious virion.

Other specific viral infections such as CMV, HIV and Enteroviruses have been the subject of trials for use of IVIG. In CMV, studies show that IVIG modifies severity of infection and

prevents CMV Pneumonia in bone marrow transplant patients. In HIV, there is a suggested beneficial effect of IVIG in HIV-infected children as well as in Enterovirus encephalitis and polymyositis. In Epstein-Barr Virus infection, uncontrolled studies showed clinical improvement with IVIG and its use may be beneficial in combination with interferon. The availability of RSV-rich IVIG licensed for use particularly in prematures, poses a problem of possible fluid overload which necessitates caution in patients with cardio-pulmonary disease. Other uses of IVIG in specific diseases include botulism, diphtheria, hepatitis A, hepatitis B, hepatitis C, measles, poliomyelitis, rabies, rubella, tetanus and varicella.

Future directions for the use of immunoglobulin therapy include development of specific IVIG for Group B *Streptococcus* especially for prematures, IVIG for *Pseudomonas* for burn patients and IVIG for HIV treatment and prevention. Monoclonal antibodies are now being tried for use alone or in combination with IVIG.

CORTICOSTEROIDS

The most common uses of corticosteroid are in allergic diseases, dermatologic diseases, rheumatoid disorders and autoimmune disorders. Its use as an anti-inflammatory agent has been beneficial in these types of conditions in which definitive therapy is not available.

Much has been known about corticosteroids and its various uses need not be discussed further. What would be our main concern is to remind ourselves about the pros and cons of using corticosteroids. The adverse effects are listed here.

ADVERSE EFFECTS OF CORTICOSTERIOIDS
Glucose intolerance
Weight gain
Osteoporosis
Hypertension
Gastritis
Cataracts
Aseptic necrosis of large joints
Growth failure
Increased susceptibility to infection
Hypothalamic hormone suppression

Those who are on prolonged use of corticosteroids must be properly informed of these adverse effects.

IMMUNONUTRITIONALS

These are dietary factors that may confer advantages to the immune system and other adaptive functions in children. Immunonutritionals are listed.

IMMUNONUTRITIONALS
Breastmilk
Vitamins and minerals such as Vitamin A, C, E, Iron, Zinc
Nucleotides
Probiotics

Breastmilk has many immunologic and protective components that have shown beneficial effects in reducing gastrointestinal and respiratory infections in the first 2 years of life. It has also decreased the incidence of middle-ear effusions in children with cleft palate.

For Vitamin A, whose functions are epithelial tissue differentiation, antitumorigenecity and immune modulation, supplementation trials have shown 39% decrease in mortality rates due to diarrheal diseases and 55% decrease in deaths due to measles. On the other hand, zinc supplementation leads to decreased prevalence and morbidity of diarrhea among malnourished children and decreased prevalence of respiratory tract infections. There are contradictory results regarding treatment of the common cold.

ISOPRINOSINE

This is a synthetic purine derivative with immuno-stimulating properties and leading to increased lymphoproliferative response. Randomized controlled trials using isoprinosine in viral infections showed that it slows early progression of HIV infection to AIDS. It may decrease morbidity to rotavirus and influenza infections. For herpes, warts and even rheumatoid arthritis results are controversial or disappointing.

SUMMARY

The increasing knowledge about immunomodulators, have shown that the immunologic responsiveness to invasive pathogens can be altered and regulated in varied ways. These are done through the use of non-specific and specific immunomodulators. However, the rational use of many immunomodulators must still await clinically significant studies.