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Lecture

Primary Immunodeficiencies and Lung Disease

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Primary immunodeficiencies, once considered extremely rare, are now increasingly recognized thanks to more knowledge and to the availability of more sophisticated diagnostic techniques. In addition, the availability of antibiotic, antifungal and antiviral drugs and of support therapy such as total parental nutrition, have contributed to prolong the survival of patients with Primary immunodeficiency who, in the past, died of severe infections during the first few months of life.

The respiratory tract is the most common target of Primary immunodeficiency, and respiratory infections and/or failure are the most frequent cause of death.

In patients affected by severe combined immunodeficiencies and T-cell defect, respiratory infections are almost always found as well and Pneumocystis carinii and Cytomegalovirus pneumonitis, abscesses of the lung containing Pseudomonas aeruginosa, are a common cause of death. HLA identical bone-marrow transplantation fully corrects the immunodeficiency in these patients (3). Correction of the immunological disorder and improvements of the respiratory infections have also been achieved in selected patients with primary T-cell defect using thymic extracts.

We have performed a trial using a calf thymic extract, Thymostimulin (TPI, Serono) in patients with various forms of Primary Immunodeficiencies.

Thymostimulin was administered at the dose of 1 mg/kg/day i.m. and then continued at the same dose 3 times a week for 3 months.

We treated 13 patients with primary immunodeficiencies and chronic lung disease with calf thymus extract; 5 out of 13 infants with T-cell defect showed immunological recovery and clinical remission which lasted for several months after interruption of the therapy (1).

More recently we have performed a double blind trial with Thymostimulin in patients with primary immunodeficiencies and recurrent herpes infections. Thymostimulin induced a significant decrease of the number of herpes simplex infections and of severity of the infections graduated with a score from 0 to 3.

The only side effect reported by us among the more than 50 patients treated with thymostimulin, was a generalised urticaria which occurred within few minutes from the thymostimulin injection in a baby affected by the Wiskott-Aldrich syndrome. This patient had IgE to cow's milk (17 PRU/ml - RAST) and this allows for speculation that, being Thymostimulin a calf thymic extract, it contains some antigens which cross-react to cow's milk.

More recently we have treated 40 patients affected by various forms of primary immunodeficiencies and respiratory tract infections with TP-5 (Ortho Pharmaceutical Corp.), a synthetic pentapeptide with the same biological activity of the whole molecule of thymopoietin (2). TP-5 was administered at the dose of 1 mg/kg/day i.m. for 2 weeks and then continued at the same dose 3 times a week for 3 months. TP-5 was capable of inducing clinical and immunological improvement in 5 infants with the DiGeorge syndrome and in 3 out of 6 patients with T-cell defect. All of these infants suffered from interstitial pneumoniae which did not improve with cotrimoxazole-trimetoprim therapy, but disappeared during the TP-5 treatment.

TP-5 was not capable of inducing any clinical and immunological improvement in patients with Ataxia-Telangiectasia, common variable hypogammaglobulinemia, severe combined immunodeficiency. 3 out of 5 children affected by hyper-IgE syndrome and severe chronic lung disease showed a significant increase of eosinophil number and IgE concentration along with a clinical deterioration during the TP-5 therapy. In addition, we have recently conducted a double blind trial with TP-5 in patients with selective IgA deficiency and recurrent respiratory infections without any immunological and clinical improvement.

Due to the fact that patients with humoral defects (agammaglobulinaemia and hypogammaglobulinaemia) are virtually unable to have an antibody response to antigenic challenge, they chronically and severely suffer from bacterial infections. These patients

almost invariably contract infections with pyogenic organisms, mainly staphylococci, pneumococci, streptococci and Haemophilus influenzae. The infections are usually controlled with antimicrobial chemotherapy. If left untreated, many of these infants develop chronic progressive bronchiectasis and, should they survive the countless infections, they ultimately die of pulmonary complications.

Today it is known that a normal serum concentration of IgG does not exclude the possibility of an abnormal level of IgG2 or IgG4, and the IgG subclasses deficiency might play an etiologic role in the chronic chest symptoms in some children.

IgA is by far the most frequently missing of all the immunoglobulin classes. According to data from the Italian Register for Primary Immunodeficiencies it is estimated to occur in 1:330 to 1:500 of the general population (4). IgA defect may occur in apparently normal subjects, however, our experiences confirm that patients with IgA defect often suffer from respiratory recurrent infections. Recently, selective deficiencies of IgG4 and/or IgG2 have been associated with IgA deficiency. The results of some studies raise the possibility that deficiency of IgG subclasses contributes directly to the severity and chronicity of these children's symptoms. Viral illnesses are frequently associated with exacerbation of asthma, and IgG subclass abnormalities might predispose to more frequent or more severe viral illnesses. Siber et al (5) have demonstrated a correlation between IgG2 concentration and antibody responses to polysaccharide antigens from the encapsulated Streptococcus pneumoniae and Haemophilus influenzae bacteria, so that chronic respiratory symptoms in children with IgG subclasses deficiency might result from an inability to clear pre-sent encapsulated bacteria or bacteria which increased in number as a result of inflammation initiated by other factors.

In the past it was believed that patients with selective IgA deficiency might form antibodies against the immunoglobulin they lacked when this was administered. Systemic reactions seen in some patients after i.v. gammaglobulin administration were attributed to circulating anti-IgA antibodies. Therefore, gammaglobulin therapy was thought to be unsuitable. More recently, it has been shown that these reactions are associated with aggregates which activate the alternative complement pathway, thus inducing anaphylactic reactions. Further studies have demonstrated that intravenous gammaglobulin preparations can be safely used also in patients with IgA defect and anti-IgA antibodies.

We have treated 23 children, aged 5-15 years, affected by agammaglobulinaemia or hypogammaglobulinaemia and severe chronic lung infections with intravenous gammaglobulin (Sandoc), 150-300 mg/kg every 3 weeks for 2 years. In these children the number of infections or fever, days in bed or in hospital dramatically decreased while IgG serum levels increased to about normal values. No severe side effects were observed.

In conclusion, the respiratory tract and especially the lung, are the most common targets in Primary immunodeficiency syndromes. Some of these disorders have an acute course often leading to an early death when the immune defect is not corrected with BM transplant or, in few selected cases, with thymic hormones.

Many patients with immunoglobulin deficiency are severely affected by chronic and recurrent respiratory tract infections, inexorably leading to bronchiectasis, but today, the early intravenous gammaglobulin administration can prevent bronchiectasis and offer such patients a totally normal life.

REFERENCES.

1. Aiuti F, Ammirati P, Fiorilli M, D'Amelio R, Franchi P, Calvani M, Businco L 1979 Immunologic and clinical investigations on a bovine thymic extract. Therapeutic applications in primary immunodeficiencies. *Pediatr Res* 13: 797
2. Aiuti F, Businco L, Fiorilli M, Galli E, Quinti I, Rossi P, Seminara R, Goldstein G 1983 Therapy with thymopoietin pentapeptide (TP-5) in 26 patients with primary immunodeficiencies. *Lancet* I: 551
3. Businco L, Rossi P, Paganelli R, Galli E, DiGilio G, Lulli P, Aiuti F 1984 Bone marrow transplantation and thymopoietin pentapeptide treatment in two infants with immunodeficiency with predominant T-cell defect. *Clin Immunol Immunopathol* 33: 123
4. Luzzi G, Businco L, Aiuti F 1983 Primary immunodeficiency syndromes in Italy: A report of the National Register in children and adults. *J Clin Immunol* 3: 316
5. Siber GR, Schur PH, Aisenberg AC, Weitzman SA, Schiffman G 1980 Correlation between serum IgG-2 concentrations and the antibody response to bacterial polysaccharide antigens. *N Engl J Med* 303: 178