Novel methods of therapy of neuroautoimmune diseases such as multiple sclerosis, neuroboreliosis as well as autism

INSTITUTE FOR BIOMODULATION MEDICINE
Gotthardstrasse, Zug, Switzerland

Abstract: The invention includes methods of treating autistic spectrum disorders, including autism, in a patient where the method includes administration of an inhibitor of gamma interferon, an inhibitor of IL-1 beta, an inhibitor of IL-6, an inhibitor of IL-12, an inhibitor of IL-18, an inhibitor of TNF-alpha, and the administration of IL-10, alone or in combination, to the patient.

SUMMARY OF THE INVENTION

The present invention includes a method of treating an autistic spectrum disorder (ASD) in a patient, the method comprising administering to the patient an effective amount of an antibody to gamma interferon. In yet another aspect of the present invention, the antibody is selected from the group consisting of a polyclonal antibody, a monoclonal antibody, a humanized antibody, a synthetic antibody, a heavy chain antibody, a human antibody, and a biologically active fragment of an antibody, wherein the biologically active fragment is a Fab fragment, a F(ab')sub.2 fragment, a Fv fragment, and combinations thereof.

BACKGROUND OF THE INVENTION

The ability of the immune system to discriminate between "self" and "non-self" antigens is vital to the functioning of the immune system as a specific defense against invading microorganisms. "Non-self" antigens are those antigens on substances entering or present in the body which are detectably different or foreign from the animal's own constituents, whereas "self" antigens are those which, in the healthy animal, are not detectably different or foreign from its own constituents.

However, under certain conditions, including in certain disease states, an individual's immune system will identify its own constituents as "non-self," and initiate an immune response against "self" material, at times causing more damage or discomfort as from an invading microbe or foreign material, and often producing serious illness in an individual.

Autoimmune disease results when an individual's immune system attacks his own organs or tissues, producing a clinical condition associated with the destruction of that organ or tissue, as exemplified by diseases such as rheumatoid arthritis, insulin-dependent diabetes mellitus, acquired immunodeficiency syndrome ("AIDS"), hemolytic anemias, rheumatic fever, Crohn's disease, Guillain-Barre syndrome, psoriasis, thyroiditis, Graves' disease, myasthenia gravis, autism, glomerulonephritis, autoimmune hepatitis, multiple sclerosis, systemic lupus erythematosus, dystrophic epidermolysis bullosa, and the like. Blocking, neutralizing or inhibiting the immune
response or removing its cause in these cases is, therefore, desirable.

Autoimmune disease may be the result of a genetic predisposition alone or as the result of the influence of certain exogenous agents such as, viruses, bacteria, or chemical agents, or as the result of the action of both.

Some forms of autoimmunity arise as the result of trauma to an area usually not exposed to lymphocytes, such as neural tissue or the lens of the eye. When the tissues in these areas become exposed to lymphocytes, their surface proteins can act as antigens and trigger the production of antibodies and cellular immune responses which then begin to destroy those tissues. Other autoimmune diseases develop after exposure of the individual to antigens which are antigenically similar to, that is cross-reactive with, the individual's own tissue. For example, in rheumatic fever an antigen of the streptococcal bacterium, which causes rheumatic fever, is cross-reactive with parts of the human heart. The antibodies cannot differentiate between the bacterial antigens and the heart muscle antigens, consequently cells with either of those antigens can be destroyed.

Other autoimmune diseases, for example, insulin-dependent diabetes mellitus (involving the destruction of the insulin producing beta-cells of the islets of Langerhans), multiple sclerosis (involving the destruction of the conducting fibers of the nervous system), and rheumatoid arthritis (involving the destruction of the joint lining tissue), are characterized as being the result of a mostly cell-mediated autoimmune response and appear to be due primarily to the action of T-cells (See, Sinha et al., Science 248:1380 (1990)).

Yet others, such as myasthenia gravis and systemic lupus erythematosus, are characterized as being the result of primarily a humoral autoimmune response (Sinha et al., Science 248:1380 (1990)). As an example, dystrophic epidermolysis bullosa has been attributed to mutations in the non-collagenous domains of collagen type VII. These mutations result in the lack of formation of the normal anti-parallel collagen type VII dimers. The mutated collagen forms epitopes recognized as "non-self" by the immune system, and therefore autoantibodies are generated, resulting in the rapid degeneration of the basement membrane of the skin (Chen, et al., J. Biol. Chem. 276: 21649 (2001)). Similarly, pemphigus vulgaris is attributed to the presence of auto-antibodies to desmosomes, specifically the desmoglein 3 protein, which are the points of intracellular contact between epithelial cells. The auto-antibodies destroy the adhesion between cells, resulting in a loss of epithelial integrity and elasticity. Nevertheless, the autoimmune diseases share a common underlying pathogenesis, resulting in the need for safe and effective therapy. Yet none of the presently available drugs are completely effective for the treatment of autoimmune disease, and most are limited by severe toxicity, except currently arising selective regulatory neuropeptides.


IFN has been found in the circulation of patients with autoimmune diseases, and it has been neutralized in vivo with antibody to leukocyte (alpha) IFN ("IFN.alpha."). Healthy people do not have interferon in their blood (Skurkovich et al., 1975). In addition, it has been shown that hyperproduced alpha IFN is found not only in the circulation of patients with classic autoimmune diseases, but also in patients with HIV infection (DeStefano et al., J. Infec. Disease 146:451 (1982)), where its presence is a predictive marker of AIDS progression (Vadhan-Raj et al., Cancer Res. 46:417 (1986)). The IFN induced by HIV has low anti-(HIV) viral activity (Gendehnan et al., J. Immunol. 148:422 (1992)).
Investigators have also shown that tumor necrosis factors (TNF alpha and TNF beta) also play a significant role in the pathology of autoimmune diseases. For example, the presence of TNF alpha has been correlated with rheumatoid arthritis (RA) (Brennan et al., Brit. J. Rheum. 31(5):293-8 (1992)), and TNF alpha has been found to be related to an increase in the severity of collagen induced arthritis in animal models (Brahn et al., Lymphokine and Cytokine Res. 11(5):253 (1992)), while it has also been shown that anti-TNF alpha antibody administration ameliorates collagen induced arthritis (Williams et al., Clin. & Exp. Immunol. 87(2):183 (1992)). TNF alpha is increased in the serum of RA patients (Holt et al., Brit. J. Rheum. 21(11):725 (1992); Altomonte et al., Clin. Rheum. 11(2):202 (1992), and both the cytokine (Chu et. al., Brit. J. Rheum. 31(10):653-661 (1992)) and its receptors have been identified in rheumatoid synovium, as well as at the cartilage-pannus junction (Deleuran et al., Arthritis Rheum. 35(10):1180 (1992)).

IFN is known to induce tumor necrosis factor (TNF) and its receptors (Lau et al., AIDS Research and Human Retroviruses 7:545 (1991)), which enhances virus replication (Matsuyama et al., Proc. Natl. Acad. Sci. USA 86:2365 (1989)). In addition to its presence in the circulation, IFNs have also been found in the cerebrospinal fluid in some patients with psychiatric mid neurologic diseases (Lebkova et al., Acta Biol. Med. Germ. 38:879 (1979); Preble et al., Am. J. Psychiatry 142:10 (1985)), as well as in patients with rheumatoid arthritis. Therefore, since healthy people do not have interferons in their spinal or synovial fluids, the inventors have suggested that one or more alpha IFNs may be involved in the development of the initial autoimmune disease response. Consequently, the removal and/or neutralization of alpha IFN has been proposed as a method of treatment of patients with autoimmune disease, including AIDS. The appearance of cytokines and autoimmunogens induced by alpha IFN and their prolonged circulation in the body is an inseparable part of the development of autoimmune disease, triggering immune dysregulation in autoimmune disease, including AIDS.

In addition to classic autoimmune disease and AIDS, autoantibodies play a pathogenic role in many other pathological conditions. For example, after cell (or organ) transplantation or after heart attack or stroke, certain antigens from the transplanted cells (organs) or necrotic cells from the heart or the brain can stimulate the production of autoantibodies or immune lymphocytes (Johnson et al., Sem. Nuc. Med. 19:238 (1989); Leinonen et al., Microbiol. Path. 9:67 (1990); Montalban et al., Stroke 22:750 (1991)), which later participate in rejection (in the case of a transplant) or attack cardiac or brain target cells, aggravating the condition. Moreover, in human autoimmune disease certain cells express abnormally elevated levels of HLA class II antigens, which is stimulated by the disturbed production of cytokines, e.g., gamma IFN alone, or gamma IFN in combination with TNF (Feldman et al., "Interferons and Autoimmunity," in IFN 9, Academic Press, p. 75 (1987).

ASD is a group of diseases with similar symptoms, the differences lying in time of onset of symptoms, how quickly symptoms develop, the severity of the symptoms, and the exact nature of the symptoms. ASD includes autistic disorder (autism), pervasive developmental disorder-not otherwise specified (PPD-NOS, which includes atypical autism) and Asperger disorder. Other similar pervasive developmental disorders include Rett syndrome and childhood disintegrative disorder. Data regarding the number of children with ASD are not clear, but rates in localized areas of the United States vary from 3.4 children per one thousand to 6.7 children per one thousand. Further, recent studies estimate that 15,000 children aged three through five years, and 78,000 children and young adults aged six through twenty-one years in the United States have autism. Rates in Europe and Asia are similar, with as many as six per one thousand children having at least one ASD.
Repeated behaviors and routines are sometimes crucial to the daily life of an ASD patient. Some behaviors may be repeated over and over again, and a change in any familiar routine, however minor, can lead to confusion if altered. The response to changes in routine actions can manifest itself as violence, either towards others or self-mutilation in the ASD patient.

Children with ASD develop at motor, language, cognitive and social skills at different rates, while children without ASD develop these four parameters of development at similar rates. As an example, a child with ASD may quickly develop motor skills while language, cognitive and social skills lag behind. Children with ASD may also learn a skill, such as speech, and have a normal vocabulary, only to stop speaking altogether at a later time.

ASD is often accompanied by other disorders. Seventy-five to eighty percent of ASD patients are mentally retarded to some extent, about one-third have varying degrees of seizures, about ten percent have Fragile X syndrome, and about one-quarter of those affected with Tuberous Sclerosis also have ASD.

The underlying causes of ASD, such as damaged brain structures and impaired nerve connections, cannot be readily corrected by existing medications. However, drugs useful in treating other diseases with similar symptoms can be useful in managing ASD, however none have been approved by the FDA for treating ASD. Medications used in the treatment of anxiety and depression, such as fluoxetine (PROZAC.TM.), fluvoxamine (LUVOX.TM.), sertraline (Zoloft.TM.) and clomipramine (Anafranil.TM.) have been used to address certain symptoms of ASD. Stimulant drugs such as Ritalin.TM. have been used to treat the hyperactivity sometimes associated with ASD. Because sensory disturbances and a seemingly imperviousness to pain often accompany ASD, research has been done to counteract the levels of endorphins in ASD patients, as it is believed that increased endorphin levels may result in suppressed physical sensation. Powerful anti-psychotic medications, such as chlorpromazine, thioridazine, and haloperidol have been used in ASD patients to temporarily reduce agitation, aggression and repetitive behaviors. However, due to serious and possibly permanent side effects, anti-psychotic medications are used sparingly and with extreme caution.

Behavioral and educational interventions are often favored over medical treatments for ASD. Many behavioral and educational treatment options focus on building skills and replacing certain behaviors with more socially appropriate actions. The most effective ASD treatment programs usually center around an ASD child’s interests and offer predictable and structured activities and environments. Further, the active and constant role of teachers, therapists and parents seems to offer the best chance in overcoming some of the social, communication, and behavioral hurdles of ASD. However, a child cannot outgrow ASD and there is no “best” course of treatment for all individuals with ASD. ASD remains a lifelong disease, and despite the success of some ASD patients in leading productive and relatively normal lives, these instances are the exception to the general rule requiring lifelong care and limited interaction with the rest of society.

Recognition of the important role of cytokines in autoimmune disease has fostered the development of a new generation of therapeutic agents to modulate cytokine activity. Preliminary results of trials in which anti-interferon polyclonal antibodies were administered to a small group of rheumatoid patients suggest improvement in both the clinical and the laboratory manifestations of the disease (Skurkovich et al., Annals of Allergy 39:344-350 (1977)). Moreover, proteins, such as polyclonal antibodies and soluble receptors targeted against interferons and TNF-alpha, are currently being evaluated in clinical trials for the treatment of RA and other autoimmune diseases. The administration of monoclonal
antibodies to TNF-\alpha. has provided encouraging early results in the treatment of patients with severe RA.

Because autoimmune diseases are complex, often characterized by multiple cytokine abnormalities, effective treatment appears to require the simultaneous administration or utilization of several agents, each targeting a specific cytokine pathway or its by-product. To meet this need, the methods of treatment of the present invention include not only the use of specific antibodies, but also provide pleiotrophic autoimmune inhibitors, including antibodies to cytokines and HLA class II antigens, and antigens for the removal of autoantibodies to target cells or DNA.

The use of these antibodies and antigens as disclosed in the present invention results in the removal, neutralization or inhibition of the pathogenic cytokine(s), HLA class II antigens, and/or autoantibody(ies) to target cells or DNA from the autoimmune patient, thereby significantly improving the quality of life of the individual.