

POSSIBILITIES TO MODULATE THE IMMUNE RESPONSE DURING INFECTIONS

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ABSTRACT

Immunomodulating drugs are important tools in the treatment of infectious diseases, especially hepatitis. The authors present different classes of immunomodulators that are currently in use. After the era of antibiotherapy and of augmentation of host defense through immunizations, the time has come for immunomodulation substances to be reevaluated. Because multidrug antibiotic resistance has turned into a major medical problem, intensive research has been done in the field of immunomodulation.

Key Words: host defense, immunomodulators, infectious diseases

During immune response in infectious diseases a considerable number of humoral and cellular factors are released. If they are released in inadequate quantities, the immune response may be either insufficient or in excess, thus leading to alterations of host structure. Nowadays, there are several therapeutic means available to modify the immune response.

Bajcetic presents three approaches that are currently used to modulate the immune response:¹

-alteration of the thresholds of immune activation. This way, the immune response can be weakened or strengthened (blockade of co-stimulatory factors; the antagonization of inflammatory cytokines or protective cytokines; inhibition of signaling cascades by small molecules).

-the modulation of antigen-specific responses (induction of regulatory cells by intravenous, subcutaneous or oral delivery of antigen; alteration in peptide ligands; formation of large assemblies from peptide and major histocompatibility complex

molecules; induction of B-cells tolerance; immune deviation from type 1 to type 2 helper T cells).

-sparing of target organs (complement and cytokines antagonization; use of anti-inflammatory agents; inhibition of matrix metalloproteases and of nitric oxide synthase).

Interference with co-stimulation and signaling chemokines and other molecules critical to immune activation is designed to restore homeostasis in the immune system and dampen the autoimmune response.²

Immunomodulatory therapy represents an important field in the treatment of infectious diseases and is more actual every day. According to Fauci's definition, an immunomodulator is a biological or non-biological substance that directly influences a specific immune function or modifies one or more components of the immunoregulatory network to achieve an indirect effect on a specific immune function. Animal studies have shown that immunomodulators are substances of varied origin: cytokines, pharmaceuticals, microbial products, and traditional medicinal plants.³

It has several years now since the immunomodulators have classified depending on their origin⁴ in endogenous, exogenous, and synthetic. Immunomodulators have been used to stimulate the defence mechanisms for prophylaxis and treatment of viral, bacteria, parasitic, and fungal diseases^{2,5} Nowadays, the field of clinical immunomodulation is

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growing fastly and it holds promise in the treatment of immunodeficiency diseases, infections, and cancer.⁶ Examples of most used immunomodulators in our clinical practice are: substances of synthetic origin (levamisol, isoprinosine, thalidomide, rodilemid, pentoxifilline), bacterial compounds (BCG, Luivac, Bronhovaxom, Urovaxom, Cantastim, Aerodin, IRS-19), and endogenous substances (thymical hormones, cytokines, cytokine antagonists, monoclonal antibodies).

We will further describe the main mechanisms of action and clinical use of the above-mentioned immunomodulators.

Levamisol is an imidazole derivative that acts by partially restoring the cellular immunity through stimulation of the T lymphocytes differentiation and maturation and normalization of effector functions of CD8 T cells and the regulatory properties of CD4 T cells. It restores the phagocytic activity of macrophages and polymorphonucleares but does not influence humoral immunity and does not act on normal functioning T cells and macrophages.⁷ Levamisol has certain qualities, however, according to our studies, the clinical benefits are limited (unpublished data).

Isoprinosine stimulates the proliferation of T lymphocytes, the activity of macrophages, the synthesis and release of lymphokines and lymphotoxins, the maturation of T and B lymphocytes, and the action of endogenous interferons and lymphokines. Isoprinosine is still in use in prolonged forms of acute A and B hepatitis and in hepatitis produced by cytomegalovirus (CMV). Our experience showed good results when using isoprinosine in treating acute CMV hepatitis and in correcting CMV-induced hypogammaglobulinemia in small babies with transplacental or perinatally acquired infection (unpublished data).

Pentoxifilline is another immunomodulator that reduces production of interferons by endotoxin-stimulated monocytes and reduces the effects of interferons and other proinflammatory cytokines on polymorphonucleares. It is indicated in severe sepsis and in HIV infection, although it has no effect on mortality rate.²

Although thalidomide was first synthesized in 1954 and was an over-the-counter sedative associated with many teratogenic and neurotoxic accidents, it is nowadays an emerging immunotherapeutic agent. It is an immunomodulator and anti-inflammatory agent, with the main effects the inhibition of alpha-interferon synthesis and release from mononuclears in the peripheral blood.⁸ Reports suggest that thalidomide has a role in the upregulation of T-helper 2 (Th2) type immunity. Thalidomide increases the production of Th2-type (humoral) cytokines (interleukin 4 and 5) and

inhibits the production of the Th1-type (cellular) cytokine IFN-gamma, in antigen- and mitogen-stimulated mononuclear cells from the peripheral blood. It enhances the cellular immune response and inhibits angiogenesis⁸. It is indicated in the treatment of HIV infection (wasting syndrome, Kaposi's sarcoma), cancer, aphthous ulcerative stomatitis, idiopathic esophagus ulcers, leprosy and tuberculosis.²

Bacterial-derived immunomodulators may be used as prophylactic or therapeutical agents in infectious diseases.^{9,10}

BCG stimulates macrophages, T and B lymphocytes, stimulates NK cell function and augments interleukin 1 production. BCG has been successfully used in the past 20 years in non-specific activation of the immune system in some forms of cancer (urinary bladder) and in infectious diseases.¹¹ Mycobacterial heat shock proteins and toxins of *Staphylococcus aureus* induce polyclonal activation of certain T cell subsets.

Other bacteria-derived compounds, such as Bronhovaxom, Urovaxom, Luivac, IRS-19, Aerodin, Polidin, Cantastim,¹² Biostim¹³ induce lymphocyte proliferation in the mucosal-associated lymphoid tissue (MALT), followed by their migration in tonsils and lungs. They also increase synthesis and release of IL5, IL6 that initiates Th2 immune response. These bacterial extracts stimulate interferon production in respiratory epithelium, enhancing Th1 immune response, increase the synthesis of secretory IgA and activate macrophages and NK cells. Indications for these bacteria-derived agents are represented by chronic respiratory and urinary infections, in association with antibiotics.¹⁴

Since the production of cytokines is modulated by several biological agents such as hormones, prostaglandins and drugs, these may also serve as therapeutic targets for immunomodulation.¹⁵ Consequently, stress^{16,17} or hormones such as cortisol, thymic extracts, melatonin⁸ may act as immunomodulatory agents. Thymus extracts may be of use in viral B hepatitis, herpes zoster, herpes labialis and chronic *Trichophyton rubrum* infections.¹⁹ Corticotherapy is frequently used as potent suppressor of the immune response with marked anti-inflammatory activity. Corticosteroids are indicated in *Hemophilus influenzae* meningitis, tuberculous meningitis and pericarditis, typhoid fever with shock and autoimmune chronic active hepatitis.²⁰ Corticosteroids have disappointing results in septic shock and acute respiratory distress syndrome.²¹

In the group of immunomodulatory cytokines, best characterized in terms of efficiency, safety and mechanisms of action are the interferons.^{1,22,23} Interferons are glycoproteins secreted by infected cells, macrophages, lymphocytes and act as a protecting

factor against cytophilic pathogens. They have antiviral activity (inhibit the translation of viral RNA into viral protein), inhibit the proliferation of malignant cells, facilitate the phagocytic functions of macrophages, increase the number of NK cells and increase expression of class I HLA antigens.³

There are different types of interferons: type I: IFN α , with 12 distinct proteins; IFN β - a single species; IFN ω - a single species; IFN κ ; IFN τ ; and type II: IFN γ .²⁴

Type I IFN have immunomodulatory and antiviral activity, while type II IFN has an antiproliferative effect. Specific cell receptors exist for the two types of IFN. IFN α and IFN β represent a link between immune memory and chronic inflammation. The majority of expanded T cell generated during an immune response is cleared by apoptosis. Prevention of death in some activated T cells enables the persistence of a memory T-cell pool. There are observations that IFN α and IFN β inhibit activated T-cell apoptosis. Although enables memory T cells to persist without antigen, excessive IFN- α or IFN- γ secretion might lead to chronic inflammation.²⁵

Interferons have several mechanisms of action. Interferons bind to specific cell-surface receptors and stimulate the cellular synthesis of specific gene products within 15 minutes: 2'5' oligo-adenylate synthetase gene, HLA Class I genes, protein kinases, b-2 microglobulin. These gene products enhance antigen presentation by the target cell and activate antiviral pathways within the cell. Suppression of viral replication and elimination of infected cells by the immune system are eventually achieved.²⁶

The available forms for clinical use are: recombinant interferon α : 2a (ROFERON A) or 2b (INTRON A) usually administered associated with antiviral drugs (lamivudine or ribavirin); natural interferon α -n3 (ALFERON N); bioengineered interferon α facon-1 (INFERGEN); pegylated interferon: PEG (40 kD) IFN- α -2a (PEGASYS) and PEG (12 kD) IFN- α -2b (PEG-Intron).²⁷

Because of their multiple effects interferons are contraindicated in severe cardiac disease, renal failure, decompensated liver disease, epilepsy, severe neurological impairment, autoimmune liver disease, uncontrolled thyroid disease, and severe psychiatric disorders, particularly depression.²⁸

The most common side effects of interferon are fever, lethargy, insomnia, diarrhea, occurring early in the course of treatment in most patients. Late side effects of interferon therapy are: depression, bone marrow suppression, thyroiditis, hypothyroidism, hyperthyroidism, and impotence, with a non-negligible impact on patients' quality of life.²⁹

Interferons are widely used in chronic infections with hepatitis B, D and C viruses, attempting to suppress the viral replication, halt the progression of liver disease and to render the patient noninfectious.

In chronic B hepatitis, indications for beginning interferon therapy are: positive HBs and HBe antigens, HBV-DNA, and elevated ALT. If signs of viral replications are absent (positive HBs with negative HBe antigen, undetectable HBV-DNA, and normal ALT), or in case of advanced liver disease or liver failure, or in immunodeficient states (HIV infection, renal failure, and organ transplantation) interferon therapy is contraindicated.²³

High response rate to IFN treatment in chronic HBV infection is obtained if active hepatitis and low serum HBV-DNA levels are present. Inactive disease, high levels of serum HBV-DNA and immunosuppression determine poor response rate. Interferons in higher doses and for longer periods than for HBV infection are used in the therapy of chronic HDV infection. Clearance of HBs antigen and cessation of HDV replication were obtained in 20% of cases and remission without loss of HBs antigen in 36% of cases. The prognostic factors for sustained viral response in chronic HCV infection are: genotype non-1, low viral load, age under 40 years, fibrosis stage, HAI higher than 10, ALT higher than three times ULN, body weight, gender. Sustained response to interferon in chronic C hepatitis is expressed by: normalization of liver enzyme levels, loss of serum HCV-RNA, improvement of inflammatory scores, and regression of fibrosis.

Pegylated interferon is the newest pharmaceutical form of interferon that proved beneficial in patients less responsive to other treatments, particularly those with cirrhosis and HCV genotype 1.²³

Interferon therapy in association with ribavirin seems to be more effective than monotherapy.

Interferon α is also used in human papillomavirus infections: condyloma acuminatum (intralesional 1-5 million units three times a week for three weeks) and recurrent respiratory papillomatosis (systemically administered).³⁰

Recombinant human interferon γ is indicated in chronic granulomatous disease, visceral leishmaniasis, lepromatous leprosy, and MAC-chronic disseminated infections in AIDS patients.³¹

In addition to interferons the following cytokines are used in clinical practice:

- IL-1 is used as a non-specific adjuvant therapy in bacterial infections trying to dampen the augmentation of the inflammatory response in sepsis.³²
- IL-2 presents as recombinant human IL-2-aldesleukin (PROLEUKIN), and is utilized in the

therapy of disseminated cutaneous leishmaniasis (intralesional) and leprosy (intradermally) where it enhances cell-mediated immunity and decreases the number of organisms in lesions, in HIV infection, raising the number of LT CD4 positive cells, and also in various malignancies.³³

- IL-10 exerts a intense anti-inflammatory effect, through the inhibition of proinflammatory cytokines. IL-10 is synthesized by TH2-type lymphocytes and upregulates humoral immune responses and attenuates cell-mediated immune reactions.³⁴

- IL-12 plays a critical role in defense against infection by intracellular organisms. It is used as adjuvant therapy in mycobacterium infections, leishmanial infections, and in HIV infection.³⁵

Another way to modulate the immune response via cytokines is by blocking their action through monoclonal antibodies against TNF α , TNF α receptors and against endotoxines, soluble receptors for IL-1, TNF α , IL-1 receptor antagonist, PAD antagonists, bradikinin inhibitors, inhibitors of iNos. Previous studies show the therapeutical effects of cytokine blockers in septic shock.³⁶

Certain immunoglobulins are used for passive immunization against various pathogens (hepatitis A virus, varicella-zoster immunoglobulin, tetanus, rabies). Intravenous immunoglobulins (IVIG) are important immunomodulators by several mechanisms: Fc receptors blockade, antiidiotype antibodies, anti-Fab2 antibodies³⁷ antibodies against cytokines or complement factors.³⁸ Immunoglobulines are used intravenously in primary immunoglobuline deficiencies, HIV infections, after bone marrow transplantation, GVH disease, cytomegalovirus interstitial pneumonia, gram-negative septicemia, premature infants and Kawasaki syndrome.^{38,39}

As a conclusion, infectious diseases represents one of the most important causes of mortality despite the progress made by the antibiotherapy, mainly due to increasing antibiotic resistance. Augmentation of host defense through immunization and passive immunization can be further enhanced by the use of immunomodulating substances. Nowadays, it is more obvious that the time has come for a reappraisal of non-antibiotic, immune response enhancing substances. The diverse array of natural, synthetic and recombinant immunomodulators discussed here demonstrated the potential of these agents to stimulate host-defense mechanisms for prophylaxis and treatment of various infectious diseases.⁴⁰ Recent studies have led to the development of new strategies for immunomodulation such as DNA and oligonucleotides vaccination⁴¹⁻⁴³, use of cytokines.^{44,45} Further research is needed to confirm the efficacy and safety of these new therapies.

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