

NON-SPECIFIC IMMUNE RESPONSE

Even though we are all exposed to various pathogens at all times, we only seldom become clinically ill. This is because we are endowed with a robust immune apparatus that is highly evolved and multi-facet with the ability to distinguish between "self" and "non-self". On escaping and by-passing the mechanical barriers like the skin and muco ciliary clearances, as a part of the antigen non-specific immune response, the foreign organisms/antigens are phagocytosed/lysed by the phagocytes or the NK cells without any cell-to-antigen specificity. Any of the cells of the non-specific immune response, namely the, neutrophils, macrophages, dendritic cells and the NK cells can attack/destroy any antigens that are non-self. The number of organisms/antigens that each of these cells of the non-specific immune response can destroy is rather modest. If the pathogen load is very high then this non-specific immune response can be easily overwhelmed.

ANTIGEN SPECIFIC IMMUNE RESPONSE

The antigen specific immune response is manifested by the helper CD4 T lymphocytes, the cytotoxic CD8 T lymphocytes (CTLs), the suppressor CD8 T lymphocytes and the B-lymphocytes. The phagocyte that has brought the foreign antigen to own its surface (inserted in the MHC class II proteins) is now called the antigen-presenting cell (APC). The antigen specific immune response as the name implies, is a highly specific reaction against a specific immunogen/antigen with a specific and particular molecular structure/configuration and is effected by a specific cytotoxic CD8 T lymphocyte (CTL) or a B lymphocyte which have a T-cell receptor (TCR) or a B-cell receptor (BCR) exactly matching and complimentary to the molecular structure/configuration

of the epitope of foreign antigen/immunogen being presented by the APC. The total repertoire of TCRs and BCRs in humans is thought to be of 3 trillion, thereby implying that we are genetically equipped to counter 3 trillion different antigens/immunogens.

APC which has brought the antigen on to its own surface physically encounters (in the systemic circulation or lymph nodes) a CD4 helper T lymphocyte which has a TCR exactly matching the epitope of the antigen being presented (inserted in MHC class II proteins), there is an interaction between the APC and this specific helper CD4 T lymphocyte. This results in activation of both the APC and the specific helper CD4 T lymphocyte. Cytokines like IL-1, TNF- α and γ -INF are released by the activated APC, while the specific helper CD4 T lymphocyte releases IL-2, IL-12, and IL-16. As a consequence of high levels of the cytokine IL-2 that acts as an autocrine hormone, this particular CD4 cell with a specific TCR matching the antigen being presented expands clonally thereby producing thousands of identical helper CD4 T lymphocytes, each with an identical TCR.

Cytokines are chemical messengers for and of the immune cells enabling them to communicate with each other and also signaling the bone-marrow-thymus axis for the development and recruitment of new immune cells in orchestrating the host immune response. Cytokines form an integral component of the immune apparatus and are central in our ability to manifest an immune response.

Whenever such activated CD4 cells from the clonally expanded pool of activated helper CD4 T lymphocytes encounter (in systemic circulation or in the lymph nodes) an CD8 CTL which also has an exactly matching and identical TCR, such an CD8 CTL would be activated and

expand clonally, again due to release of the TH1 cytokines like γ -INF, IL-2, IL-12 and others. All human cells, when infected, have the ability to present the invading antigen/immunogen on its own surface as a part of MHC class I protein. Thus whenever an activated CD8 CTL encounters any cell that shows a particular antigen on its surface as a part of MHC class I proteins, which is matching to its own TCR, then such an infected cell would be lysed by this CD8 CTL through release of chemicals like perforin and other reactive free radicals. CTL mediated antigen specific immune response is the effector response against intracellular pathogens/ antigens like HIV and TB.

In case the infecting antigen is extracellular, the effector immune response is through activation of B-lymphocytes.

There is a constant balancing action between host defenses on one hand and the pathogen virulence and numbers on the other hand which keeps the pathogens at bay and prevents the development of an active clinical disease. Whenever, the host immunity is 'compromised' or 'decreased' the pathogens would get the upper hand and an active clinical disease would ensue. This is best exemplified by infection with HIV and the diseases that then follow.

Fate of Infection

In most of the cases of tuberculosis, primary complex heals by itself. Only 5 to 10% of the infected population develops clinical tuberculosis in their lifetime. It is well known that before the availability of effective treatment for tuberculosis about 30 to 50% of the clinical tuberculosis patients regained their health spontaneously and recovered from their illness without any specific treatment. With HIV and TB coinfection, as the host immunity goes down there is 30 to 60 times more probability of developing TB than otherwise.

Monotherapy with various drugs or inadequate and incomplete drug regimens have strongly contributed to the creation of drug resistant and multi DR-TB. Such TB strains are mainly prevalent in regions with weak national TB programs or poor socioeconomic environments. Today world has become global village and any this resistant pattern from one part of the world can easily travel to any other part in no time, making it global problem.

The thought of immunotherapy is not recent. Robert Koch tried tuberculin with the same hope of altering immune response. Tubercle vaccine by Friedmann for prevention and treatment of tuberculosis and use of BCG to boost immunity are a few another examples of earlier

attempts. Both these failed, but the search continued. There was a small gap with the availability of effective chemotherapy.

Immune system is a complex network of positive and negative feedback loop that acts by the means of secretion of numerous cytokines. Immunomodulation is any process that can alter immune system of an organism by interfering with its function. Modulation of immune system may result in suppression or augmentation of immunological reactivity. Apart from being specific suppressive or stimulative activity, certain agents have been shown to possess activity that can normalize or modulate the pathophysiological process. It involves homeostasis between Th1 (cell mediated) and Th2 (humoral). Also it leads to fine tuning of inhibitors, activators and regulatory signals ensuring immunostasis and agents restoring this balance are classified as immunomodulator.

Factors responsible for altered immune response:

1. Prolonged use of steroids.
2. Use of immunosuppressant drugs.
3. HIV infection
4. Diabetes
5. Foods containing
 - i. Chemical fertilizers
 - ii. Insecticides
 - iii. Pesticides
 - iv. Preservatives

6. High Stress

Broadly, there are two ways to increase the host immunity:

- Increasing the immune response to specific microbial antigens (the vaccine approach).
- Non-specifically stimulating the host immune mechanism (the immune based/immunomodulatory approach)

The *major goals* of immunomodulator and immune-based therapies include:

- Potentiating the host's immune system to better control of TB;
- Strengthening the patient's native immunity against a variety of opportunistic infections.
- Oppose the biological effects of the bacilli on the host by —
 - Inducing the production of beneficial cytokines and amplifying their biological effects

- Inhibiting the production and biological effects of harmful pro-inflammatory cytokines
- Stimulating the overall generation and activity of immune cells by stimulating the bone marrow thymus axis.

The immunomodulators are useful in:

- Preventing infections to proceed to disease state
- Preventing the occurrence of secondary infections
- Achieving early control of infections in conjunction with specific chemotherapy.
- Achieve early clinical response in terms of weight gain and reduction in toxemia.

In resource-limited settings like ours, the use of cytokines or allogeneic and syngeneic bone marrow transplantation, donor lymphocyte infusions, which are sparingly available and are very expensive, are practically beyond the reach of most of our patients.

Immunomodulators available:

- Levamisole
- Immunoglobulins – IgG
 - Polyclonal
 - Monoclonal (Vaccines)
- Herbomineral drugs (Reimun)
- Mycobacterium W vaccine
- Vaccine approach (Bronchomunal)
- Cytokines/Leukotrienes.
- Donor lymphocyte infusion
- Synergic bone marrow transplant

Levamisole

Levamisole has been studied in Europe for many years as an Immunomodulator, and its primary use have been as an anti-parasite. It restores depressed immune function and an immunoadjuvant, since its effect on the immune system depends in part on the presence of antigenic stimulation. Levamisole can stimulate antibody formation to various antigens, enhance T-cell responses by stimulating T-cell activation and proliferation, potentiate monocyte and macrophage functions, including phagocytosis, chemotaxis and increases motility, adherence, and chemotaxis. Levamisole can stimulate a normal and a depressed immune system, and is often classified as both an immunoregulator and immunostimulant. It affects humoral and cell-mediated immunity and has been

shown to restore neutrophil motility in patients with herpes simplex virus infections. Levamisole affects T-cells to a greater degree than B-cells, leading to cutaneous reactivity to delayed-type hypersensitivity antigens and improvement in helper, suppressor, and cytotoxic T-cell functions. Dadi at Italy carried out the first clinical study and subsequently Mohanty at Sewree TB group of hospital tried it in cases of tuberculosis with encouraging results in suspected drug resistant tuberculosis and relapse cases.

Immunoglobulins

Immunoglobulins are proteins produced by cells of the B-lymphocyte lineage that are the major effector molecules of the humoral immune system. Immunoglobulin molecules are antibodies that react with specific antigens, although in many circumstances, the specificity of a given immunoglobulin antibody is unknown. Immunoglobulin preparations from human blood were first used in clinical medicine in 1952 to treat immune deficiency conditions. At that time, the only available preparations required intramuscular (IMIG) administration. In the past two decades, several immunoglobulin preparations for intravenous administration have become available. Although initially used for immune deficiency states, intravenous immunoglobulin (IVIG) has also been utilized as a prophylactic and therapeutic reagent in a variety of other conditions. The use of IVIG has undergone tremendous growth in the past several years. This rapid growth in use is the result of improvements in the preparations of IVIG, which have led to reduced morbidity and reports of its benefits in a number of unexpected circumstances. IVIG has been used in such diverse diseases as primary immunodeficiency, pediatric AIDS, infections in low birth weight infants, bone marrow transplantation, chronic Lymphocytic leukemia, idiopathic thrombocytopenic purpura, Kawasaki syndrome, and demyelinating polyneuropathies.

Various mechanisms may be important in the different therapeutic uses of IVIG, including (1) replacement therapy for primary and secondary immunodeficiencies (2) specific passive immunotherapy and (3) management of specific inflammatory and/or immunologic disorders.

A study of its use in cases of relapse and suspected drug resistant tuberculosis was done at JJ Hospital under the guidance of KC Mohanty where between 1986 to 1988, 80 patients were given immunoglobulins for 3 months along with 2nd line AKT drugs. It was observed that the group receiving immunoglobulins had a better

success rate (88 % compared with 72%). Also 105 fresh cases of tuberculosis with HIV were treated with AKT (without ART) and immunoglobulins and earlier tuberculin conversion and sputum conversion along with quicker clinical improvements were noted. Also they had significantly lower opportunistic infections in immunoglobulin treated group.

Immuvac

Mycobacterium W is a nonpathogenic, rapidly growing organism. It was identified as a unique organism as an immunomodulator for leprosy. Multibacillary leprosy is associated with anergy to *M. leprae* antigen. The anergy is very specific to *M. leprae* antigen. Even when patients are cured for leprosy using multidrug therapy (MDT), anergy to *M. leprae* antigen persists. It is due to poor Th1 type response.

In search of a potent immunomodulator to enhance Th1 response, different *Mycobacteria* were evaluated. All were evaluated for their ability to enhance Th1 response (human) as determined by blast cell transformation as well as lymphoproliferative response. The research gradually narrowed down the number of organisms as a potential candidate for final selection as a potent Th1 response enhancer. Ultimately only one organism, *Mycobacterium W.*, was found to be the most potent of all and so it was selected for further evaluation and clinical application.

MW also shares antigens (particularly 13 KDa protein), which are specific for immunity with *M. tuberculosis*. This antigen sharing results in provide protection against Tuberculosis and drug resistant tuberculosis. Controlled clinical studies conducted at Ahmedabad by Naresh Patel, at Udaipur by Luhadia, and at Mumbai by Mohanty have uniformly shown the earlier sputum conversion and clinical response in both newly-diagnosed as well as proven cases of drug resistant TB and TB-HIV co-infection.

Reimun

From the time immortal, we have been using herbomineral preparations as immunomodulators in ayurvedic medicine. We have various compounds available. These herbs have been shown to differentially modulate the cytokine profile, inducing and amplifying the effects of certain cytokines while at the same time

inhibiting others. With the advent of HIV and with increased prevalence of DR and MDR-TB, there is resurgence of research activity in the traditional medicine of Chinese and Indian origin, to use these drugs as an adjuvant to potentiate the immunity of host for HIV and TB. Reimun is a herbomineral formulation comprising of such immunomodulating and Immuno Potentiating herbs.

Deshpande tried this preparation in HIV cases at Sir JJ Hospital, Mumbai where it was found to improve weight of the patient, CD4 counts and quality of life of HIV patients. Subsequently it was tried for TB and MDR TB cases.

CDC Atlanta, FDA USA and NIH USA have recommended to carry out controlled research trials in traditional medicines of Chinese, Indian and Arabic origin.

50 cases of suspected drug resistant tuberculosis were put on this preparation along with second line AKT at Mumbai by Mohanty and Reimune group had better success rate in comparison to the other group They had higher weight gain, better symptomatic improvement, earlier sputum conversion and more complete radiological resolution.

Patient Selection

- i. Immunocompromised host.
- ii. Advanced disease with co-morbidities.
- iii. On immunosuppressant therapy for associated diseases.
- iv. Patient who fails to respond in spite of being on appropriate therapy.
- v. Patients who develop newer lesions on treatment.

Monitoring

1. Earlier sputum conversion.
2. Earlier clinical improvement.
3. Better radiological clearance.
4. No relapse of disease.

Allergy and Immunology Society of USA states that: Immunomodulators holds key to the future treatment. The choice of immunomodulator will depend on affordability and acceptability of the patient and the experience of the treating physician.