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Review Article

A PERSPECTIVE TOWARDS VACCINATION AGAINST ATHEROSCLEROSIS

Dr Mohd Nasir Mohiuddin[1], Dr Sana Afreen[1], Dr M.Kaleemullah Khan[2], Nusaibah Ahmed Khan[3], Dr Mir S Adil[1], Dr. Swati Chacham[4]

[1]Pharm D, inter, Dept. of Paediatrics, Princess Esra Hospital, Hyderabad.

[2]MD, General Medicine, Associate Professor, Dept. of General medicine, Deccan college of Medical sciences, Princess Esra Hospital, Hyderabad , Andhra Pradesh, India.

[3]Health information management professional, University of Illinois at Chicago.

[4]MD, D.M., Neonatology, Asst. Professor, Dept. of Pediatrics, Deccan college of Medical sciences, Princess Esra Hospital, Hyderabad, Andhra Pradesh, India

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For Correspondence
Email ID:
muhammed_nasser7788@yahoo.com

Abstract:

Atherosclerosis is a disease of the blood vessels characterized by plaque buildup in the arteries. Immunization is the process by which an individual's immune system becomes fortified against an agent. Atherosclerosis is similar to inflammatory/ autoimmune diseases like rheumatoid arthritis and multiple sclerosis. Data from the previous studies suggest that these diseases may be treated by vaccination. It has been reported that by using monoclonal antibodies against specific antigens, passive immunization confers athero-protective effects. Atherosclerotic lesion formation in LDL receptor (-/-) (LDLR (-/-)) mice was significantly reduced by monoclonal IgG preparations reactive to cardiolipin or LDL. It was recently shown that atherosclerosis in animal models was reduced by a recombinant human IgG antibody against an MDA-modified apoB-100 derived peptide antigen. It is believed that oxidized LDL which causes intimal inflammation and foam cell formation have a key role in atherosclerosis. Neoepitopes are the antigenic sequences that are normally absent or concealed but which become available after the oxidation of LDL. Observations from several studies have shown that immunization changes favorably the composition of established plaques, indicated by decreased plaque inflammation and increased collagen content. Immunization against many infectious diseases completely prevents development of the disease; however it will not completely prevent development of atherosclerosis. The studies performed so far have suggested that immunization may reduce development of atherosclerosis by 50-60%. However, many questions need to be answered such as vaccine stability, safety, durability of effects, efficacy endpoints etc.

Introduction:

Atherosclerosis is a complex, slowly progressing chronic inflammatory disease that develops at sites of lipid accumulation in large and medium sized arteries. Inflammatory and immune responses contribute to the initiation, progression and destabilization of atherosclerotic lesions.[1, 2] The involvement of the immune system can be highlighted by the presence of inflammatory cells, activated immune cells, various molecules and cytokines to recruit immune cells, complements, and immunoglobulins in the lesions.

Accumulation of low density lipoprotein derivatives in arteries is one of the most essential factors causing development of atherosclerosis.[3, 4]

Studies from the past suggest that increased adventitial and plaque neovascularity, observed commonly in murine and human atherosclerosis, plays a vital role in advancement and destabilization of atherosclerosis.[5]

The treatment of atherosclerosis is based upon the combination of lipid lowering therapies and anti-inflammatory drugs. Still, the formation or progression of atherosclerotic lesions cannot be inhibited fully. In various other disease pathologies a very effective strategy called vaccination is used, in which the body is challenged with the offending protein or microorganism so as to create a highly specific humoral immune-response. [6]

Immunization:

Immunization is the process by which an individual's immune system becomes fortified against an agent (known as the immunogen).Immunization can be divided into active or passive immunization. Immunomodulation therapy aims at exploitation of the atheroprotective aspects of the immune system to modulate atherosclerosis via an active or passive immunization strategy. [7]

Active immunization: It occurs naturally when the body is exposed to certain immunogens, antigens or microbes. It also occurs artificially in the case of vaccination. Such exposure to immunogens, antigens or microbes results in the production of antibodies (antigen specific). [1]

Active immunization with antigens related to low-density lipoprotein: The beneficial effect of p210 immunization depends on cellular immune responses. [8]

Passive immunization: It is the transfer of humoral immunity (as a result of ready-made antibody transfer) from one individual to other. [6]

Atherosclerosis is similar to inflammatory/ autoimmune diseases like rheumatoid arthritis and multiple sclerosis. Data from the previous studies suggest that these diseases may be treated by vaccination.[9]

It has been reported that by using monoclonal antibodies against specific antigens, passive immunization confers atheroprotective effects. Atherosclerotic lesion formation in LDL receptor (-/-) (LDLR (-/-)) mice was significantly reduced by monoclonal IgG preparations reactive to cardiolipin or LDL.[8]

It was recently shown that atherosclerosis in animal models was reduced by a recombinant human IgG antibody against an MDA-modified apoB-100 derived peptide antigen. In phase-I human trial this antibody was proved to be safe, however in primate model it showed anti-inflammatory activity. Although the feasibility of passive immunization was suggested by these studies to modulate atherosclerosis, it still awaits confirmatory clinical studies for human application.[8]

Atherosclerosis and Immunity:

The immune system can be broadly divided into innate and adaptive immunity which are distinct yet overlapping, but both immunities modulate atherosclerosis. Innate immunity reacts rapidly in recognizing common pathogen-associated microbial patterns, such as unmethylated CpG DNA motif and lipopolysaccharides in gram-negative bacteria. It includes macrophages, natural killer (NK) cells and mast cells. For its effect or mechanism it uses complements, various cytokines or chemokines, and cell-mediated cytotoxicity. Adaptive immunity reacts slower than innate immunity and recognizes specific antigenic epitopes more specifically. Its cellular components include T and B cells. It uses cytotoxic T cells, antibodies, antibody-dependent cell mediated cytotoxicity, chemokines and cytokines.

A group of pattern recognition receptors of innate immunity are the Toll-like receptors

(TLR). Exogenous infectious triggers interact with TLRs which leads to transcription of several acute inflammatory genes. The acute innate immune response is characterized by the eventual release of inflammatory cytokines. TLR4 and other members of the TLR family are expressed by macrophages and endothelial cells in murine and human atherosclerotic lesions.

Atherosclerosis, plaque inflammation and circulating inflammatory proteins in mice is reduced by the interference in innate immune signaling through genetic disruption of TLR4 or its downstream signaling adaptor molecule (myeloid differentiation factor 88).

A naturally occurring IgM antibody with the T15 idio type might have an atheroprotective role. The IgM antibody is produced by the self-renewing B1 cells without T cell or thymic involvement; such natural antibodies recognize the phosphorylcholine head group present in the phospholipid moiety of oxidized low-density lipoprotein (LDL), apoptotic cells, and the cell wall of pneumococcus. They reduce the uptake of oxidized LDL by macrophages and attenuate murine atherosclerosis. [7]

The concept of a vaccine for atherosclerosis:

As many serious infectious diseases have been eradicated with the help of vaccines, vaccination has been tested against various non infectious chronic inflammatory or auto immune diseases such as cancer and Alzheimer's disease. It is believed that oxidized LDL which causes intimal inflammation and foam cell formation have a key role in atherosclerosis. Polyunsaturated fatty acids are oxidized into phospholipids and cholestryl esters which generate breakdown products such as malondialdehyde and 4-hydroxy nonenal. Together with amino acids containing free amino groups in apolipo protein B100 which is the main protein component of LDL, they form covalent adducts. Apo lipo protein B100 is degraded into numerous peptide fragments by the oxidation of LDL. As a result of these modifications it is thought that oxidized LDL is a target for the immune system. In healthy individuals and patients with cardiovascular disease, several clinical studies have shown the presence of circulating auto antibodies to oxidized LDL; however the relationship between the antibody titer and cardiovascular disease has been inconsistent.

Neoepitopes are the antigenic sequences that are normally absent or concealed but which become available after the oxidation of LDL. To identify the potential antigenic epitopes, the structure of apolipo protein B100 component of LDL was studied. These epitopes could be responsible for the atheroprotective effects of immunization with oxidized LDL. Among the various potential antigenic epitopes, only 102 have been found to be associated with an antibody response in pooled human serum many observations have raised the tantalizing possibility of atheroprotective vaccination strategy based on certain specific apolipo protein B100 related peptide epitopes. The efficacy of this approach in the prevention of early atherosclerosis lesions when used before significant lesion development have been demonstrated by most of the experimental studies of immunization with oxidized LDL and peptide antigens specific for oxidized LDL. However, it has to be established whether immunization is beneficial after lesions have already formed. Many investigations have been carried out to know if the immunization slows plaque progression and induces stabilization of existing plaque. [1]

Limitations:

Observations from several studies have shown that immunization changes favorably the composition of established plaques, indicated by decreased plaque inflammation and increased collagen content.[4] Immunization against many infectious diseases completely prevents development

of the disease, however it will not completely prevent development of atherosclerosis. The studies performed so far have suggested that immunization may reduce development of atherosclerosis by 50-60%. [10]

Conclusion:

A novel approach to the management of atherosclerotic cardiovascular disease is represented by the immunomodulation responses involved in atherosclerosis with the help of vaccines and passive immunization with antibodies, particularly to apolipoprotein-B100-related peptide. [6] Several studies have shown a possibility in preventing atherosclerosis by vaccination.[11] However, many questions need to be answered such as vaccine stability, safety, durability of effects, efficacy endpoints etc. [8]

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