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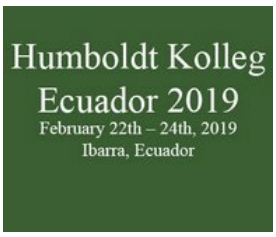

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REVISION/REVIEW

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Enzyme Replacement therapy with Pegademase Bovine for Human Adenosine Deaminase Primary Immunodeficiency

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ABSTRACT

Adenosine deaminase deficiency (ADA) represents an immune system disorder producing abnormalities in humoral and cellular immune responses due to the lack of adenosine deaminase (ADA) enzyme. PEG-ADA therapy tries to counteract ADA deficiency by conjugates conformed of numerous mono-methoxy polyethyleneglycol chains linked non-covalently, and ADA enzymes, which are bound by lysine residues. PEG-ADA protects from any proteolytic attack, and presentation of antigens, increasing their lifespan within the organism. Enzyme replacement therapy with PEGylated ADA provides metabolic correction and improvement in immune function and clinical parameters. Its effectiveness is confirmed by the increase of B and T lymphocytes in questionable time ranges.

Keywords: adenosine deaminase deficiency (ADA), severe combined immune deficiency (SCID), pegademase bovine (PEG-ADA), vasculitis.

INTRODUCTION

Primary immunodeficiency diseases (PI) are a set of more than 350 rare, chronic disorders in which part of the body's immune system is missing or functions incorrectly. One of them is the Adenosine deaminase (ADA) deficiency. ADA is an inherited disorder that damages the immune system and causes severe combined immunodeficiency (SCID). Adenosine deaminase deficiency is the result of the mutations in the ADA gene. The function of this gene is supplied instructions for producing the enzyme adenosine deaminase. This enzyme is found throughout the body but is most engaged in lymphocytes. ADA enzyme takes care of eliminate a molecule called deoxyadenosine, which is produced when DNA is broken down. Mutations in the ADA gene reduce or in turn

eliminates the activity of adenosine deaminase allowing the buildup of deoxyadenosine to levels that are toxic to lymphocytes[1]. In order to treat this type of immunodeficiency, a wide range of techniques was used, including hematopoietic stem cell transplant that is curative but dependent on a good donor match. Other therapeutic options include enzyme replacement therapy (ERT) with pegademase bovine (PEG-ADA). PEG-ADA was first used to treat ADA deficiency in 1986 and to date, more than 150 patients worldwide have received this treatment and it is known that PEG-ADA is well tolerated and can restore immune function to protective levels but long-term end product suggests that immune recovery is incomplete. The precise role of PEG-ADA beside other treatment options is still to be determined but to date, it has allowed stabilization of patients awaiting more definitive treatment and clinical well-being in individuals treated for longer periods[2].

Human ADA deficiency: an expanding clinical phenotype

Vasculitis

Vasculitis is the main clinical display of ADA with small and medium-sized arteries affected. From cutaneous and central nervous system manifestations are found in 75% and 50% of patients, respectively[3]. The skin lesions of cutaneous correspond to non-granulomatous necrotizing arteritis, nonspecific rashes, and subcutaneous nodules. The common neurological event in ADA is the lacunar ischemic infarct in the deep- brain nuclei, midbrain and brain stem involvement. ADA is an integral disease and other organs can be affected by the vasculitis or inflammation. Such is the case of renal manifestations include renal artery aneurysm and also arterial hypertension[4].

Immunodeficiency and autoimmunity

Since the beginning of ADA were known mild immunodeficiency with low IgM levels as a clinical feature in 5 patients[5]. Notably, low IgG and IgM levels are usual features of ADA, with or without concurrent findings of vasculopathy. Across studies that quantified immunoglobulins, low IgG and/or IgM levels are reported in ~67% of DADA2 patients. It is known that both B cell intrinsic and extrinsic factors may commit to the low immunoglobulin levels. The pathophysiology of the immunodeficiency in ADA2 is unclear however it is attractive to speculate a parallel with the pathophysiology of ADA1 deficiency. In ADA1 deficiency, periodic herpes virus infections are also common together with progressive lymphopenia, elevated IgE, and autoimmune phenomena. The autoimmune phenomena in ADA2 are less usual but have been observed in some patients in the form of systemic lupus and autoimmune cytopenia[6].

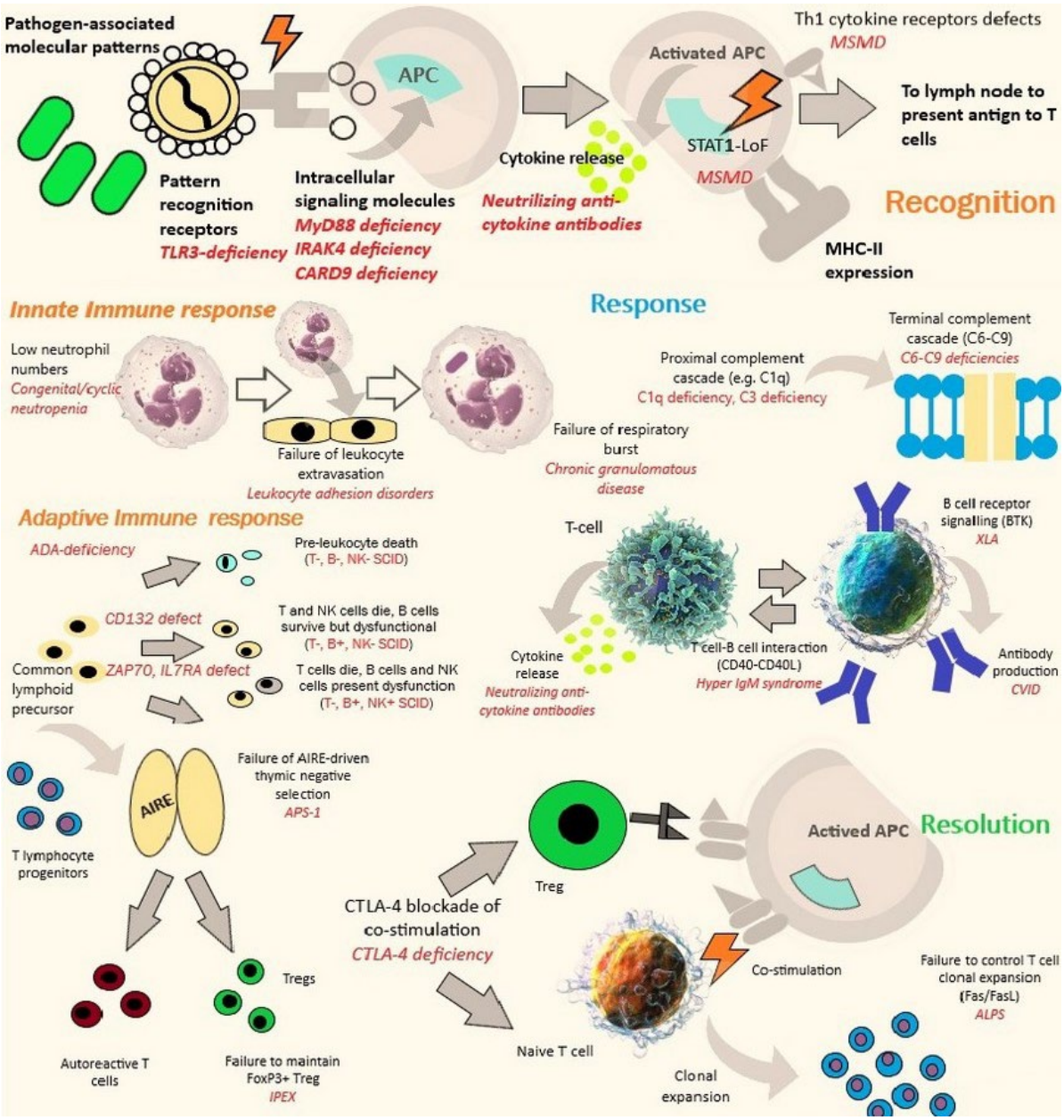

Figure 1. Classical immunological recognition, response and resolution involving primary immunodeficiency mechanisms (Benavides K. and Lovato N, 2019).

Genetic testing for ADA

Actually, there are three main management options to treat ADA deficiency: hematopoietic stem cell transplant (HSCT), ERT and gene therapy. HSCT is a highly successful and curative procedure if a matched related donor is available but it falls if a matched unrelated donor is undertaken[7]. More recently somatic gene therapy for the correction of ADA deficiency has evolved. In this way, the procedure involves gamma retroviral mediated introduction of the human ADA gene into autologous bone marrow progenitors and then the infusion of cells back to the patient following mild chemotherapy getting immune reconstitution and metabolic detoxification with stable engraftment of transduced hematopoietic cells[8].

Currently, the use of PEG-ADA provides another treatment way for ADA SCID. In contrast to HSCT, it is not a curative therapy but needs periodic intramuscular administration. Nevertheless, the effectiveness of PEG-ADA in correcting metabolic and immunological conditions and more importantly in promoting clinical comfort in patients qualifies it a significant option in the care of patients.

PEGylation implies the covalent attachment of numerous strands of monomethoxy polyethylene glycol (PEG) to an enzyme or protein. The attachment of PEG to ADA through lysine residues offers a lot of therapeutically beneficial properties to ADA by alteration of its physical and chemical properties[8]. In the same time, molecules are protected from cellular capture, proteolytic attack, renal clearance, antibody binding, and antigen presentation. Also, PEGylation diminishes the immunogenicity of a protein which helps to enlarge its circulating life[9].

PEG-ADA absorption, distribution, metabolism, and excretion depend on the patient conditions, dose and administration routes. Broadly, this conjugate is administered continuously using intramuscular inoculation[10, 11]. In a period of 1 to 3 months, patients receive 60 U /kg/week, posterior of the first administration, the dose depends on the patient response[12]. PEG-ADA biological effect tends to appear in 1 or 2 days approximately[10, 11]. After maintaining the patient with stable doses of the conjugate, the levels of ADA in the plasma are verified to report a clinical status change.

Immune reconstitution

PEG-ADA therapy is practical in leading a reconstruction of the innate and adaptive immune system. This regeneration is led by cells that mediate humoral responses, involving plasma B cells and memory cells, which secrete antibodies to attack pathogens, forming conjugates. The reconstitution of humoral response gives way to the start of specific cellular response, such as the formation of lymphocyte progenitors in the bone marrow, which develop entering in a stage of immature T lymphocytes in the thymus, and finally mature and active T, capable of giving rise to several more clones[11]. Normally the formation of B lymphocytes is evidenced by their increase over several weeks, performed by proliferative IL-2 that induces their formation[10]. Patients treated with PEG-ADA therapy are also prone to develop hemolytic anemia (drug-induced), or thrombocytopenia, which makes up the decrease in platelets[4].

On the other hand, many of the patients who undergo treatment by administration of PEG-ADA do not respond efficiently to therapy; this lack of response is linked to the conditions of the trafficker, or the development of anti-ADA IgG inhibitory antibodies, which will be discussed toward[4].

Effects of PEG-ADA on systemic disease

Studies involving murine with ADA-deficiency demonstrated that pulmonary conditions are caused by immunodeficiency principles; As expected, a large part of the rodents died from respiratory diseases Some studies involving murine with ADA-deficiency demonstrated that pulmonary conditions are caused by immunodeficiency principles; As expected, a large part of the rodents died from respiratory diseases[13,14]. Immune deficiencies due to irregular adenosine signaling trigger a range of pathologies, but pulmonary pathologies commonly occur, affecting processes of alveogenesis, causing enlarged alveoli and severe pulmonary inflammations[13].
With these experiments, it was shown once again that the biological effect of PEG-ADA in the organism depended on the doses applied. Relatively low doses did not give significant changes in the immune reconstruction, but they appeased some phenotypic aspects of the pulmonary affections[14]. On the contrary, the reduction of metabolic alterations in the thymus and spleen was achieved by the application of high doses[13].

Side effects

During the treatment period, anti-ADA antibody is developed, which seeks to bind to PEG-ADA and eliminate it from the body. In the case of animals, these type antibodies have an IgM isotype, and in humans, an IgG isotype,

regardless of the conformation of their heavy chains, represents a great challenge in therapy, restoring the immune reconstitution achieved. At present, the mechanism of anti-ADA antibody is not known with certainty because no studies have been conducted with humans, however, in previous investigations with groups of 17 patients, more than half had high concentrations of anti-ADA IgG antibody in the plasma suppressing its therapeutic effect. Hemolytic anemia, thrombocytopenia (platelet decrease) and erythema (erythrocytes increase) at the injection site are some of the side effects that occur when starting treatment with PEG-ADA[7,13,14].

CONCLUSIONS

The importance of bear in mind the defect of an enzymatic deficiency that leads to the accumulation of toxic metabolites lies in that it can affect different organs and systems, mainly the immune system. Therefore, the success of the therapy remains in the diagnosis and administration of timely treatment before the set of serious infections for proper detoxification and recovery of the immune system. Therefore, the development and use of PEG-ADA has provided a significant alternative option for the treatment of patients with ADA deficiency. In addition, the rapid metabolic detoxification afforded by high-level enzyme replacement allows clinical stabilization of patients and provides longer-term treatment options when no suitable donor is available.

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