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Anti IL-6R drug activity in case of castleman disease

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ABSTRACT

Castleman disease is a rare disease, the reason for the induction of this disease is unknown but as per the lab investigations data, it was found that in patients who are suffering from this disease has shown rise in the levels of the IL-6, CD levels and some other cells which are important for growth. It has been divided into types based on the impact area and intensity of the damage. Lymphadenopathy is the main symptom of this disease. Actually, Interleukin-6 is a multifunctional cytokine that is critical for T/B-cell differentiation and maturation, immunoglobulin secretion, acute-phase protein production, and macrophage/monocyte functions. Signaling of IL-6 cytokine plays an important role in the formation of the Castleman disease, it can be activated with the help of the IL-6 and gp130. Anti IL-6 agents play a major role in the inhibition by blocking the key regions that favor for the disease.

Keywords: HHV, Hyperplastic follicles, JAK/STAT system

INTRODUCTION

Castleman disease (CD) is an uncommon disease of lymph nodes and related tissues sometimes associated with human immunodeficiency virus (HIV) and human herpes virus 8 (HHV-8). It is a heterogeneous (caused by any one of multiple numbers of alleles or non-allele (locus) mutations) groups of lymph proliferative disorder. It was first specified by Dr. Benjamin Castleman in a patient with a solitary hyperplastic mediastinal lymph node with a regressive germinal centre. [1] It is distinguished into two type's mainly localized (unicentric CD or UCD) and generalized lymphadenopathy (multicentric CD or MCD).

Unicentric Castleman disease

It is most common CD. It occurs only in the single group of the lymph node region.Regions like abdomen and chest are the common regions. Patients with the unicentric Castleman disease are mostly asymptomatic usually for some times but after it prolongs it leads to the enlargement of the lymph node and ultimately that leads to the enlarged lymph nodes in the chest will show results like smaller in the breathing tube size which are going into lungs and causes breathing problems. If the enlarged nodes are in the abdomen, the person might have pain, a feeling of fullness, or trouble eating. This type of lymph nodes can be easily removed by surgical procedure

Multicentric Castleman disease

Multiple castle man disease occurs in the multiple regions of the lymph nodes, it may be any region of the lymphoid tissues. This type of the disease is observed in the immune compromised patients who are suffering from the HIV, tuberculosis and some other disease status. A person with the MCD

conditions shows the symptoms like fevers, infections, and abnormalities in the lab reports. Multicentre CD is further divided into HHV (Human herpes virus)-8–positive and HHV-8-negative MCD. [2]

Diagnosis

In the case of the UCD condition, it can be easily discovered by the enlargement of the lymph node on the particular region by impeding into the surrounding organs.

Whereas the HHV-8 positive MCD does not have any of the officially recognized diagnostic tests in such conditions it can be found by the recording of the inflammatory responses, biopsy, microscopic test and some other. Microscopic study of the lymph nodes of the patients with the Castleman disease shows as hyaline vascular (Follicles that are regressed, or depleted of germinal centre cells, Mantle zones that are expanded with small lymphocytes arranged concentrically in an "onion skin" fashion), plasma cell(hyperplastic follicles, Increased interfollicular plasma cells) and sometimes it may be as both that is mixed, by observing the microscopic structure of the lymph nodes type of the Castleman disease can be found.[3]

Pathophysiology

HIV associated condition

In the case of HIV associated infections, MCD will be present.MCD in case of the HIV is rare but it has an efficiency to cause severe danger i.e. Is fatal lymph proliferative disorder .in these conditions patients shows the systemic symptoms along with symptoms like splenomegaly, cytopenia, and diagnosis of this conditions shows, which is characterized by interfollicular plasma cell infiltration and Angio follicular hyperplasia. [4] If HHV-8-infected cells are stained with the immunohistochemical it reveals a large number of cells with plasmacytic differentiation that are mostly present within the mantle.

HHV-8 associated condition

Proposed a unified model of the path physiology of CD representing the different known and suggested mechanisms involved in that disease. VEGF plays a key role in the vascular proliferation which is a main concept in the CD actually HHV-8–infected cells will secrete vIL-6(viral interleukin-6) which have the potentiality for the production of the VEGF and this endothelial cells are the main source of the IL-6 production, so VEGF (vascular endothelial growth factor). In HHV-8 CD patients, an undefined upstream stimulus might be responsible for IL-6 production.

IL-1 is also a factor which enhances the production of IL-6 through the NF- B signaling pathway. Dysregulation at any level can lead to overproduction of IL-6, which has a pivotal impact on the disease. [5]

Role of IL-6

Interleukin acts as both the pro inflammatory cytokine substance and anti inflammatory myokine substance, produced from the T-cells, B-cells, endothelial cells, and some other cells. IL-6 induces the secretion of the hepcidin hormone from the liver, which interferes negatively with the absorption and the use of the iron which leads to the development of the chronic disease. It also helps in the production of the proteins which can trigger the inflammatory action. Cell targets of IL-6 are T, B-cells, epithelial cells, hepatocytes, monocytes/macrophages. Retroviral transduction of the coding sequence of murine IL-6 into mice bone marrow resulted in the development of a CD-like syndrome with fever, anemia, leukocytosis, hypoalbuminemia, polyclonal hypergammaglobulinemia, marked splenomegaly, and diffuse lymphadenopathy[6] studied the effect of blocking IL-6 in transgenic mice carrying human IL-6 cDNA using an anti–IL-6 receptor (IL- 6R) monoclonal antibody. Control mice developed plasmacytosis, mesangial proliferative glomerulonephritis, leukocytosis, thrombocytosis, and anemia. Mice who received the monoclonal antibody did not develop these symptoms and lived longer.

Signalling

IL-6 shows its action with the help of the two molecules they are IL-6R also known as IL-6Rα and gp130 also referred to as IL-6Rβ. IL-6R plays a major role in ligand binding but in the case of the signal transduction, it has a minute role. The cytoplasmic gp130 has a dominant feature for intracellular signaling, and also contains JAK (Janus kinase) which is a nonreceptor tyrosine kinase that transduces cytokine-mediated signals via the JAK-STAT pathway through which downstream signaling cascades are initiated. When IL-6 binds to mIL-6R

(membrane-bound IL-6R), homodimerization of gp130 is induced, and a high-affinity functional receptor complex of IL-6, IL-6R, and gp130 is formed.IL-6R is cleaved into the soluble IL-6R (SIL-6R) this is done by the help of the enzyme called ADAM (a disintegrin and metalloproteinase)-17 or by alternative splicing, can also bind with IL-6, and then the complex of IL-6 and sIL-6R can form a complex with gp130 (Figure 1)[7] .This unique receptor signaling system is termed IL-6 trans-signalling [8] . mgp130 (membrane-bound gp130) is expressed ubiquitously in the body. Therefore the IL-6–sIL-6R complex could, theoretically, stimulate most cells in the body. [8]

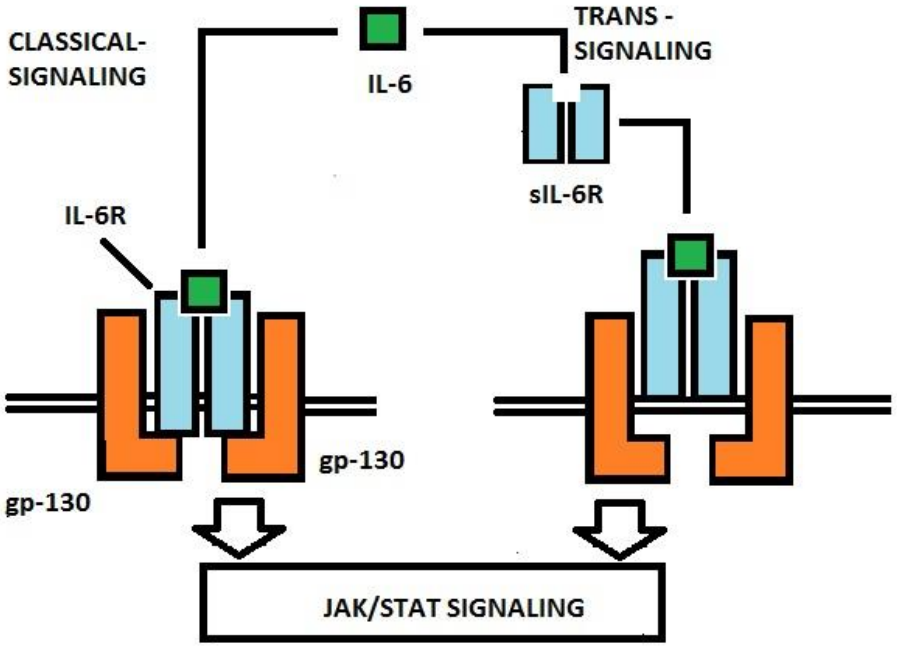

FIG 1: Mechanism of the IL-6 signaling.IL-6R also as membrane bound IL-6R (mIL-6R): interleukin-6 receptor, gp-130 glycoprotein-130, sIL-6R: soluble interleukin -6 receptors.

Actually in order to counter this mechanism of stimulation of the high IL-6 cells it can be done by the soluble gp130 (sgp 130) which will be found freely in the body in large amount, it forms a complex with the IL-6and sIL-6R it leads to the inhibition of the binding between IL-6- sIL-6R to that of the mgp-130. So sgp 130 acts as a natural inhibitor of IL-6 signaling. Where as in the case of the Castleman disease inhibitory signaling has been stopped that leads to the over stimulation of the IL-6 agents in the body.

TREATMENT

Castleman disease IL-6 agents are high which has a capacity to cause disease to produce So IL-6 receptor blocker will be as an effect of the treatment [9] .Anti IL-6 receptor antibodies (tocilizumab) have shown a good therapeutic output and its marketed for the CD. It can be produced by the complimentarily-determining region from a mouse anti–human IL-6 receptor monoclonal antibody is grafted to a human-IgG framework and shifted into Chinese hamster ovary cells for production. Its mechanism will be started by binds to the IL-6R or the soluble IL-6R (sIL-6R), which helps in IL-6 trans-signaling, preventing the binding of IL-6 to the membrane it leads to the loss of IL-6 binding that reduces both classical and trans-signaling and termination or reduction in the activity of the JAK/STAT system, leading to damping of inflammation locally and systemically. It was administered intravenously at a dose of 8 mg/kg every 2 weeks.

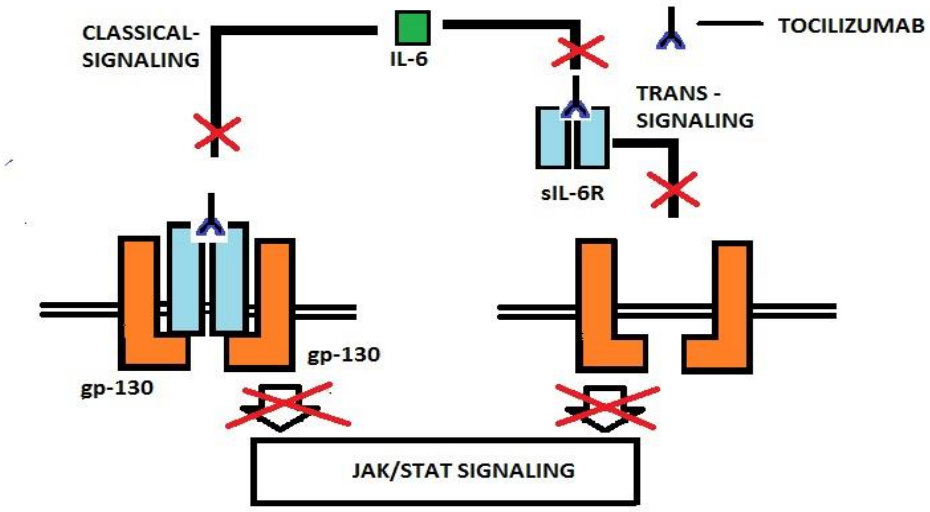

FIG: 2 Mechanism of action of the tocilizumab, it binds to the membrane bound IL-6R region and soluble IL-6R region, hence signaling is inhibited.

CONCLUSION

Treatment for CD is not easy unless or until is properly diagnosed then only it can be treated progress can be controlled, so in order to do this, all more research need to be done for better treatment of this disease. The anti-interleukin-6 (IL-6) monoclonal antibody siltuximab is the drug approved by us and European countries for the treatment of the multicentric Castleman disease for the first time. Castleman disease collaboration network is playing a key role in the scientific discovery and support to the researchers.

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