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USE OF PROTEASE INHIBITORS IN THE TREATMENT OF INFECTIOUS ANTERIOR UVEITIS CAUSED BY HSV THYMIDINE KINASE MUTANTS.

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ABSTRACT Infectious anterior uveitis also known as Iritis, is an inflammatory response in the iris due to 1° or 2° DNA virus such as HSV infection. Normally, when treated with oral Acyclovir (ACV) the infection gets resolved under 8 weeks, with seasonal re-occurrences upto an year or two with varying frequencies. However, in some cases, ACV therapy has been observed to have no effect on the infection. Such cases are thought to be caused by HSV Thymidine Kinase (TK) mutants. Loss or alteration in the viral TK gene makes them ACV insensitive. In such conditions, protease inhibitors, which prevents assimilation and envelopment of the secondary viral membrane and subsequent exit from the host cell by lysis, have been observed to have a better response to the infection leading upto almost full recovery.

KEYWORDS : Iritis, HSV, Protease-inhibitor.

INTRODUCTION:

Iritis, amongst a plethora of causative agents, is mostly caused by HSV-I; HSV-II viral strains (HSV= Herpes Simplex Virus) [1]. People with a history of previously occurring chronic epinasal or dermal HSV infection in the facial region are mostly at risk, as they carry the viruses in the trigeminal ganglion located at the middle cranial fossa almost throughout their lives. The symptoms include redness in the cornea, inflammation in cornea and iris, photophobia, blurred vision, watery eyes, irritation, stromal keratitis with keratin precipitates (KP) and high intra-ocular pressure (IOP) which may lead to glaucoma. The most common line of treatment in such cases is oral ACV coupled with corticosteroids to help resolve the redness, irritation, KP cells and fluid discharge and IOP regulatory drugs to prevent the onset of glaucoma. In more than 80% of cases, this line of treatment leads to complete cure in about 8weeks to an year or two (in cases of severe infections) [2]. However, in less than 10% of all patients globally, it has been observed that ACV therapy has little or no results in curing the infection. Patients complain of having monthly re-occurrences with symptoms persisting upto 3 or more years. These observations have led us to the HSV-Thymidine Kinase mutants. These mutant strains of HSV show no signs of inactivity in presence of ACV as ACV activation is dependent on a functional copy of viral TK gene which in these mutants are absent or greatly altered, leading to an inactive and non-functional ACV and a persisting viral infection.

MODE OF ACTION OF ACV:

ACV is an guanosine analogue which hampers with the process of viral DNA replication. ACV, in order to become active must be converted to its tri-phosphate form. The first phosphorylation process is completed by the products of the viral TK gene. The following two phosphorylation events are completed by the host cell TK gene products. The ACV-triphosphate form is an active competitor of viral DNA Polymerase enzyme. ACV-triphosphate is actively incorporated in the nascent viral DNA strand where it occupies the origin of replication in the viral genome preventing the DNA Polymerase to bind at the replication origin and initiate further replication process. This stops the viruses from multiplying and infecting more healthy cells, thus imposing a check on the spread of the infection [3].

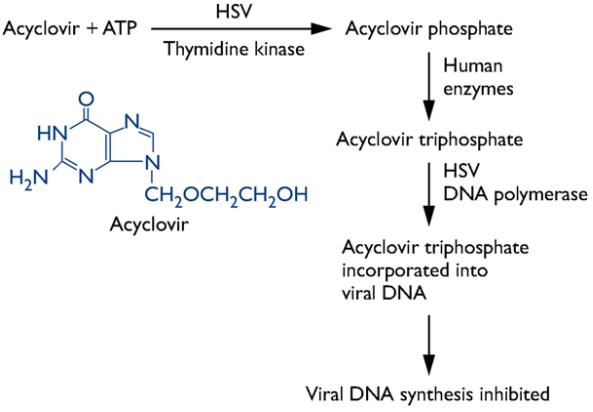

Fig 1 : Mechanism of action of ACV against HSV infection.

WHY ACV IS INEFFECTIVE AGAINST HCV THYMIDINE KINASE MUTANTS:

Nucleotide substitutions, insertions, deletions in the viral TK gene confers resistance to the ACV drugs. In TK deficient viruses, the TK gene is altogether deleted resulting in complete loss of gene products aiding the ACV phosphorylation event. Nucleotide substitutions and insertions result in an altered TK gene products (known as TK altered virus) to which the AVC cannot recognize and bind. The later mutations also alters the activity of the viral DNA Polymerase enzyme. These mutations blocks the first phosphorylation event of ACV activation process, rendering the drug useless. Most of these mutations occur in the G or C homopolymer repeats, which are known to be hotspots for mutations [4].

PROPOSED REMEDY USING PROTEASE INHIBITORS:

Protease inhibitors are found to be very efficient in preventing the spread of infection caused by HSV Thymidine Kinase mutants. Unlike ACV, they are neither nucleoside mimics nor competitive inhibitors of viral DNA Polymerase. Instead, they prevent the assimilation and envelopment of the secondary viral membrane and the subsequent exit from the cell through lysis. A protease is basically a Trypsin molecule that viruses such as HSV use for their maturation. Protease inhibitors selectively binds to the Trypsin residues and blocks the proteolytic cleavage pathways of protein precursors necessary for the formation of the secondary viral envelop and the viral DNA Polymerase. Protease inhibitor drugs such as Nelfinavir have been found to have good results against HSV Thymidine Kinase mutants and are readily available in Indian as well as global markets upon prescription by registered physicians [5].

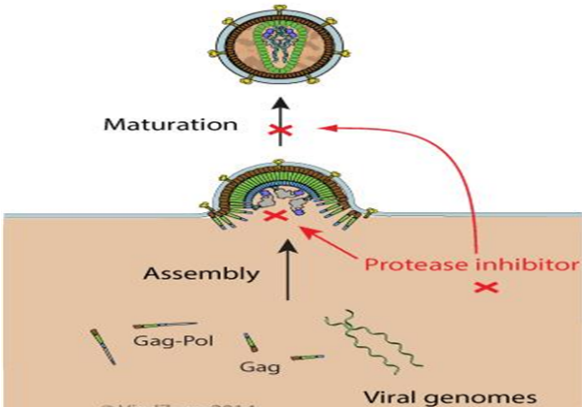

Fig. 2 : Mechanism of action of protease inhibitors.

PRECAUTIONS:

Protease inhibitors if used over long periods of time or in high dosages may lead to Type-I Diabetes Mellitus and kidney stones [6]. Liver and Kidney function tests along with blood sugar measurements are to be undertaken before drug administration.Optical Coherence Tomography (OCT) along with Fluorescein Angiography are to be routinely performed to assess the condition of the retina during protease inhibitor therapy by the ophthalmologists.

CONCLUSION:

Eyes are one of the most critical sensory organs in humans. Infections in the eyes are not only difficult to diagnose and treat but also very tedious. Protease inhibitors offer a welcome relief to those suffering from mutant viral strains outside the therapies offered by conventional drugs, saving both precious time, money and mental agony. However, care should be taken to assess the general health conditions of the patients before introducing the drugs to prevent unwanted health hazards in other vital organs arising from the side effects of the concerned drug.

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