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Emerging Trends in Treatment of Hepatitis B with Modern Medicine

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ABSTRACT :-

Hepatitis B virus (HBV) is a little DNA virus with peculiar characteristics like retroviruses. It belongs to the Hepadnaviridae family and is a verus prototype. The goal of treating chronic hepatitis B (CHB) is to permanently suppress

HBV replication in order to prevent hepatic decompensation, liver cirrhosis, and/or hepatocellular carcinoma and lengthen survival because active hepatitis B virus (HBV) replication is the primary cause of hepatic necroinflammation and disease progression. Hepatitis B can be treated with a variety of therapies like IFN based therapy, NUCs therapy. The necessity of HBV blood testing and subsequent anti-HBV vaccination in the prison population has been emphasised by the Centers for Disease Control and Prevention. All prisoners were advised to get the vaccination, providing a chance to protect against HBV infection in a group at high risk. New information suggests that other biologic drugs, like tumour necrosis factor (TNF)-inhibitors, may also cause HBV reactivation.

KEY WORDS:- Hepatocellular carcinoma, Necroinflammation, IFN therapy, NUCs therapy, Emphasised, TNF-inhibitor, HBV.

1.INTRODUCTION:-

The hepatitis B virus(HBV)is the cause of the liverillness known as hepatitis B. HBV is categorised into ten genotypes (A to J) and is a member of the Hepadnaviridae family [1].it is transfer through perinatal transmission from infected mothers to newborns as well as by contact with infectious blood or other body fluids (such as semen or vaginal secretions during sexual activity).(2)

Due to the almost 300 million people who have a chronic HBV infection, the hepatitis B virus (HBV) represents a serious threat to global public health. Hepatocellular carcinoma (HCC) and liver cirrhosis are lifelong risks for these patients. The nucleos(t)ide analogues (NAs) and pegylated interferon alpha (Peg-IFN-) groups of medicinal medicines are currently approved for the treatment of chronic HBV infection and can stop or prevent this unwelcome progression. Both, though, have drawbacks. The nucleos(t)ide analogues, on the other hand, are oral, second-generation reverse transcriptase inhibitors, such as tenofovir disoproxil fumarate (TDF), entecavir, and the recently approved tenofovir alafenamide (TAF). They have been shown to effectively lower but not completely eradicate HBV DNA levels, stop the disease from progressing to cirrhosis, reverse liver fibrosis, and even cause cirrhosis.(3) In the absence of treatment, chronic hepatitis B (CHB), which is characterised by persistent HBsAg (the hepatitis B virus' surface antigen) for six months or longer, poses a threat to the entire world.(4)

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2. HBV Serological Spotter

Acute and chronic hepatitis B virus infections present with a variety of symptoms.(5)The severity of an acute infection can range from subclinical to clinical, and it can result in either icteric (30%) or anicteric (70%) hepatitis. Acute infection can cause fulminant hepatic failure in a limited percentage of individuals (0.5%) due to immunologic lysis of the virus-infected hepatocytes. Long-term viral antigen exposure can cause both direct viral cytotoxicity and immune-mediated liver harm in patients with persistent viral infections. Although some individuals may continue to be asymptomatic carriers, this persistent viral assault might eventually result in chronic hepatitis, cirrhosis, or hepatocellular cancer. The detection window is 30 to 60 days, while the incubation period is between 30 and 120 days.

Hepatitis B continues to be a major global cause of illness and mortality, although being preventable by vaccination(6). According to the World Health Organisation, 257 million people worldwide had chronic hepatitis B in 2015, and 887,000 people passed away from the disease (due to cirrhosis and hepatocellular carcinoma) (7).

Hepatitis B is spread both horizontally (through contaminated body fluids, such as those from sexual intercourse or needlestick exposure) and vertically (from mother to child at birth) in endemic areas. Compared to infected adults, people who contract chronic infection are more likely to do so while they are younger. A small percentage of people with hepatitis B also have HIV or hepatitis D. The presence of HBV is necessary for the subviral agent known as hepatitis D to replicate.(8)

3. THE LIFE CYCLE OF HEPATITIS B VIRUS

The bile salt transporter known as sodium taurocholate cotransporting polypeptide (NTCP) , which is located on the surface of hepatocytes, is where the virion attaches to start the HBV life cycle (Figure 1). The pre-S1 domain's stretch of amino acids (2-75) has a role in virus binding.(9) Neutralising antibodies against HBsAg, the cornerstone for the prophylactic immunisation against HBV, can stop the contact between the virus and its receptor. Currently, research is being done to find substances that can prevent new hepatocytes from becoming infected with HBV. Two potential routes for cell entrance after attachment have been proposed (Figure 1): endocytosis or fusion of the HBV envelope with the plasma membrane. In any case, the end outcome is the transport of naked nucleocapsids to the nuclear pores from the cytoplasm. It is believed that HBV enters the nucleus through the intricate network of the endocytic route.(10)

The nucleocapsid disassembly occurs at the nuclear pore followed by translocation to the nucleoplasm of the released relaxed circular HBV DNA (rcDNA). Within the hepatocyte nucleus, the rcDNA is converted into cccDNA mentioned previously (11)

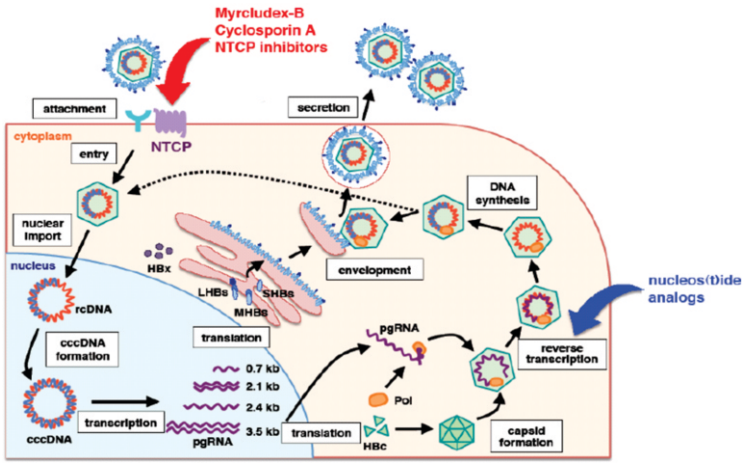

Figure 1

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The phases in the life cycle of the hepatitis B virus (HBV), from viral entrance into hepatocytes to release of mature virions into the extracellular environment. Investigational antiviral agents' target areas are highlighted. Hepatitis B surface antigen, covalently closed circular DNA, sodium taurocholate cotransporting polypeptide, and hepatitis B e antigen are examples of these terms.

The variable positive strand is finished, the viral polymerase that was covalently attached to the 5? end of the negative-strand (-) DNA and the short RNA oligomer from the 5? end of the plus-strand (+) DNA that is used to prime (+)-DNA synthesis are removed, and then the ends of the two now complete strands are ligated together. With a plasmid-like shape and organisation as a minichromo some thanks to connection with histone and non-histone proteins, cccDNA is remarkably durable in this form [12]. The activity of numerous nuclear transcription factors, including transcriptional repressors, coactivators, and chromatin-modifying enzymes, controls how it functions [13]. There are binding sites for liver-specific transcription factors in almost all of the viral genome's regulatory elements, as well as in its ORFs [14]. Therefore, the cccDNA makes use of the cellular transcriptional machinery for viral morphogenesis and protein synthesis. The HBV cccDNA molecule is exceptionally stable and can stay in the nucleus for the whole life of the hepatocyte. Antiviral medication can redsuce intrahepatic cccDNA levels, however this kind of HBV DNA seems resistant to being eradicated [15], until complete cell death. The development of novel treatment strategies aimed at suppressing, decreasing, or better yet deleting the cccDNA reservoir may be aided by the identification of variables impacting the stability and transcriptional activity of the cccDNA.

The packaging of the pgRNA and reverse transcriptase into the spontaneously forming nucleocapsids, which takes place within the cytoplasm, is the subsequent step in HBV replication. The HBV DNA polymerase uses the encapsidated pgRNA as a template for reverse transcription, which results in the production of viral rcDNA. By using the nucleotide sequence of the side bulge of the epsilon encapsidation signal, which is located at the 5? end of the DNA molecule, the polymerase starts the manufacture of a three nucleotide long DNA primer that is covalently bonded to the terminal protein.(16)

4. DIAGNOSIS AND TREATMENT OF HEPATITIS B

Peg-IFN treatment and long-term use of third-generation nucleotide analogues have both been recommended [17] as ways to arrest the progression of chronic hepatitis B and prevent the expected liver damage. It is obvious that long-term NA treatment will result in virological remission and an improvement in the liver's histology. However, quitting NA comes with a substantial risk of virological recurrence [18]. To better understand antiviral therapy for CHB and its impact on illness remission and relapse, taking into account the mechanism of action, duration, and host variables, we will analyse a number of research in this systematic review. In order to treat CHB, two subcutaneous interferon (IFN)-based medications and seven oral nucleos(t)ide analogues (NUC) have received approval. Lamivudine (LAM), adefovir (ADV) and telbivudine (LdT) have been rendered almost obsolete because of issues of drug resistance, whereas entecavir (ETV), tenofovir disoproxil fumarate (TDF), tenofovir alafenamide (TAF) and pegylated interferon (Peg-IFN) are the first-line drugs of choice for anti-HBV therapy [,21,22,23,24].

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4.1 IFN-Based Therapy

After a limited term of therapy, Peg-IFN benefits CHB patients with HBeAg positivity as well as those with HBeAg negativity by having both antiviral and immunomodulatory effects. ALT normalisation was obtained in 41% of HBeAg-positive CHB patients treated with subcutaneous Peg-IFN 180 g per week for 48 weeks, HBeAg seroconversion with HBV DNA 400 copies/mL in 32% of patients, and HBsAg seroconversion in 3% of patients, according to studies [25]. Peg-IFN therapy had worse outcomes when administered for a shorter time (24 weeks) and/or at a lower dose per week (90 g) than is advised [26]. Additionally, a mean three years interval follow-up study in those HBeAg-seropositive patients 52 weeks following Peg-IFN LAM treatment found that 81% of those initial HBeAg loss had sustained its response and 27% of those initial HBeAg non-responders had experienced delayed HBeAg loss. It is noteworthy that 11% of patients overall and 30% of first responders successfully lost HBsAg after treatment [27]. The durability was further reported by Wong et al. at five years after therapy, revealing 69% of the initial HBeAg non-responders, followed by delayed HBeAg seroconversion, with a 60% overall HBeAg seroconversion rate [28]. ALT normalisation, HBV DNA 20,000 copies/mL, HBV DNA 400 copies/mL, and HBsAg loss were all found to be 59%, 43%, 19%, and 3%, respectively, after six months post-treatment (Peg-IFN therapy at 180 g/week for 48 weeks) assessment in HBeAg-negative CHB patients, according to the phase III global trial [29]. Long-term follow-up revealed that HBsAg reduction occurred in 5% and 12% of patients treated with 1-year Peg-IFN LAM at one year after therapy and 31% and 23% of patients treated with 1-year Peg-IFN LAM at five years after therapy, respectively [30].

5. Problems of Current Therapy

5.1 IFN-Based Therapy

All therapeutic guidelines recommend it as one of the first-line treatments, however because to its subcutaneous injection, poor tolerability, and substantial adverse effect profile, it hasn't been widely used. Additionally, it should not be used in those who have hepatic decompensation, immunosuppressed conditions, serious concomitant disorders, or who are pregnant. Therefore, Peg-IFN has only been applied to around 5% of patients in the actual world, and it is only favoured by young patients who plan to have children soon and those who reject long-term NUCs treatment.

5.2 NUCs Therapy

Since NUCs have no direct effect on the cccDNA of the HBV-infected hepatocytes but can substantially lower HBV DNA, it is typically necessary to continue long-term NUCs therapy indefinitely in order to sustain a virological response [21,22,23,24]. According to a mathematical modelling study, three to four decades of NUC therapy would be necessary to establish a functional cure [31]. The next subsections provide an overview of the various issues and drawbacks of lifelong NUC therapy that have surfaced and have been thoroughly explored [32].

5.2.1. Rarely Achieved: The Ultimate Goal of HBsAg Loss A significant 10-year HBsAg loss rate of 2.1% and an annual incidence of just 0.22% were found in a large multinational multicenter long-term ETV/TDF therapy cohort trial involving 4769 patients [33].

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5.2.2. Issues with Cost and Drug Resistance The use of low genetic barrier NUCs therapy, such as LAM, ADV, or LdT, has been linked to the emergence of resistance mutants [34], which can lead to hepatitis, hepatitis flare-ups, and even potentially fatal hepatic decompensation [35]. The cost of long-term NUC therapy was also insurmountable for residents of resource-constrained nations or regions, such as Asia [36].

CONCLUSION :

According to my research even though disease knowledge is the key to lowering the disease burden, hepatitis B is a serious public health issue in India. The majority of disease cases develop silently, and when decompensated CLD or HCC has already formed, patients typically present at severe disease stages. Since a full recovery is not achievable with the medications now on the market, the goal is long-term suppression of the virus by protracted therapy, which can itself result in subpar adherence to treatment and therapy costs that are prohibitive. In the end, this is what causes inadequate disease control, infection progression, and dissemination.

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