REVIEW

Pakistan Journal of Medical and Biological Sciences
www.pjmbs.com

Direct acting agents: A new strategy to combat HCV: A review

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Abstract: Hepatitis is medical term used for the inflammation of liver tissues by infection of viruses and by the excess use of alcohols, poisons, and certain medications. Four kinds of viruses are responsible for four types of hepatitis. It may occur due to attack of HAV (Hepatitis A), HBV (Hepatitis B), HCV (Hepatitis C) and HEV (Hepatitis E). Hepatitis A is the inflammation of liver by hepatitis A, virus (HAV), Virus has ability to reduce action of antibodies by using exo-somal membranes of infected host cells. Recent research reveals that more than 200 species of small mammals are infected by HAV. Hepatitis B is also the inflammation of liver by hepatitis B virus, (HBV). Approximately 1/3 of the world's population is affected by hepatitis B virus, (HBV). Despite the early discovery of hepatitis B Virus, it is substantial burden for the global world. Hepatitis E is an acute, self-limiting and inflammatory liver disease caused by hepatitis E virus (HEV). Hepatitis D is the inflammation of liver tissues infected by hepatitis D virus (HDV) which is also called delta virus. Inflammation of liver by hepatitis G virus is known as hepatitis G. Its virus spreads by blood products and contamination of blood. As hepatitis C leads to hepatocellular carcinoma, therefore it is necessary to find new strategies for it's effective management.

Keywords: hepatitis C, Treatment strategies, inflammation, subtantial burden, acude Hepatitis.

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INTRODUCTION

Hepatitis C is an infection of liver caused by HCV. According to World Health Organization (WHO), 3% of world population is infected with HCV and the number of new cases continues to rise, more than 80% of cases leading to chronic hepatitis, hepatocellular carcinoma and liver cirrhosis (1-2). Majority of newly effected patient have no symptoms but clinical feature, jaundice is present in 25% of patient infected by acute hepatitis C. Infected person with acute hepatitis C also have malaise, nausea and right upper quadrant. In chronic hepatitis c, the infected person mostly have symptom of fatigue but other less common are nausea, myalgia, weakness, arthralgia, and weight loss (3).

Hepatitis C Virus, a single-stranded RNA, Flaviridae family virus in the Hepacivirus genus has two untranslated regions at its 3′ and 5′ends of its single strand which flanked 9.6 kb of genome and it contains one open reading frame for encoding a polyprotein of nearly 3000 amino acids. A peptidase (host signal) in the structural region and proteases encoded by viral genes in the nonstructural region cuts the polyprotein into 10 isolated proteins. The structural proteins form the viral important particle that are core protein and envelope which contains glycoproteins E1&E2 and p7, NS2, NS3, NS4A, NS4B, NS5A, and NS5B are non-structural proteins in HCV. During active phase of its infection owing to rapidly replication HCV virus produces almost ten trillion virion particles per day. (4). Liver cells (hepatocytes) are primarily infected by HCV and is released into the circulation (5) It has predominantly cytoplasmic life cycle except other RNA viruses. It is thought that there is a compromise in gene and chromosomes stability due to DNA damage and accumulation of oxidative stress in a setting of controlled cell cycle checkpoint control and forward cell division, to make the genomic basis for the lethal transformation. Indeed, changes in protein kinase (MAPK) signaling, are detected in incurable HCV infection that governs both cell metabolism and growth (6)

Intracellular oxidative stress markers have also

been detected to be high in patients with incurable HCV disease as in HCV transgenic mice (7). Overall, it is thought that participation between direct virus–host cell and chronic inflammation relations triggers the lethal hepatocytes transformation (8).

Diagnosis

Hepatitis C virus is categorized in six genotypes that diverse in their nucleotides conformation or sequence by 30–35%. They have multiple subtypes that vary in their nucleotides arrangement by 20–25% (9). HCV 1a and 1b genotypes are the most extensive genotypes in the Western Europe and United States, chase by genotypes 3 and 2. By disparity, genotypes 4 and 5 are familiar in Egypt and South Africa respectively and genotype 6 is universal in Southeast Asia. By cloning of hepatitis C virus genome, antigenic sites and B cell epitopes were detected(10). Recombinant proteins and prepared peptides having these immunodominant epitopes were the sources as the antigens in immunodiagnostic assays, ahead to the formation of importantly presence of supplemental assays and screening for anti-HCV IgG (11,12) However, these estimation cannot recognize that an antibody positive person has active HCV disease, since anti HCV IgG may be observable in persons who have determined infection and are no lasting viremic. Nucleic acid testing for exposure of HCV RNA leftover the gold stander for investigating active HCV infections. However, for performing NAT laboratory needs skilled and qualified technical staff, expensive reagents and accessories, committed procedure places, and availability of plasma serum and pristine serum. As reason these demands, NAT is not regularly performed in several clinical laboratories. Presence of a serological assay not positioned on NAT but suggestive of active infection should further help in recognition of HCV infected patients and accredit referral to care. A serological assay planted on apprehension of Hepatitis C virus core antigen has shown a promise in this regard (13).

Treatment of HCV

Different strategies have been used for the treatment of HCV. Herbal medicines were initially used but the success for eradication of virus was very low. Interferon therapy has been widely used for this purpose. Recently, direct acting antiviral agents have shown their potential for eradication of HCV in hepatitis.

Herbal treatment

Hepcinal, the eastern or herbal medicine is used to cure hepatitis C. hepcinal pills have the potential to wipeout HCV and gives firmness to the liver to work properly and has its role for detoxification. Hepcinal constituents should apply to reduce the viral haul deliberately and after 3 months constantly use of Hepcinal, the viral haul is reduced to the minor level and patient is complete cured from disease. As such the HCV in the minute frequency of existence damage the liver and sustains for all the time, but the toxicity indication is controlled in fidelity (14)

Allopathic treatment

Familiarity of composition of HCV polymerase and HCV protease has conceded structure based narcotic depiction for establishment of inhibitors for these enzymes. An idea for initial direct acting antiviral, that was a protease inhibitor, was formed in 2002. This was an innovation in hepatitis C medicine discovery (15). All Hepatitis C virus has protease enzymes; NS2-3 & NS3-4A, helicase; NS3 and NS5B RdRp vital for its reproduction and for medicine discovery targets. Therefore, direct antiviral agents along with NS3 (protease inhibitors), nucleotide correlative and non-nucleoside obstacle of the RNA-reliant RNA polymerase and NS5A obstacle, were formed (16)&(17)

Sofosbuvir is a nucleotide equivalent NS5B polymerase obstacle with identical in vitro action against all hepatitis C virus genotypes (18). A dose of sofosbuvir (400 mg) with PEG interferon ribavirin (for half to a month) emerged in rates of uninterrupted virologic response of 87-92% in formerly untreated patients of hepatitis C virus genotype 1 infection (19). Infected person with genotype 4 or 6 infections also had maximum degree of uninterrupted virologic counter for a 24 week dose of sofosbuvir with peg interferon ribavirin (19). All untreated patients infected with

hepatitis C has genotype 2 or 3 infection with a constant virologic response in 12 weeks of medication using sofosbuvir along with ribavirin (with or without peg interferon)(20).

Simeprevir is a first generation and second wave drug having antiviral activity against genotype 4 and 1. EMA and FDA have approved this drug for therapy of HCV-1 and also with combination along with other DAAs.

Daclatasvir is a drug of NS5A protein inhibitor that works against hepatitis C (21). Its use has been approved by FDA and EMA for treatment of hepatitis C. Paritaprevir in 2015 in combination with dasabuvir and ombitasvir, and ledipasvir with sofosbuvir were approved. Three other drugs may be approved in future; sofosbuvir with velpatasvir, grazoprevir with elbasvir and ABT 530 plus ABT 493 combination therapy. Many other DAAs are under the last stage of development. Development of drugs for hepatitis C has become very fast due to the shorter duration of treatment. It has become now 12 weeks instead of 24 weeks (22).

Interferon has a vital role in treatment of chronic hepatitis C infection. Interferon alone or combined with ribavirin is used now a days for patients with cirrhosis because it increases patient's thrombocytopenia and neutropenia. In interferon therapies trial very low portion of patients with advance liver diseases are found which are infected with hepatitis C. There is very low focus on treatment of hepatitis C related cirrhosis with interferon (23). By attaching a polyethylene glycol chain to alpha 2a interferon, a modified peg interferon alpha 2a was formed (24). Now it is observed that peg interferon alpha 2a has similar effects on hepatitis C patient as has interferon alpha 2a combined with ribavirin.

Effect of sofosbuvir on physiological parameter

The most effective treatment for acute hepatitis C is peg interferon alpha 2a and ribavirin that can achieve competes of 55% sustained viral eradication (Sciascio et al., 2010). This therapy has negatively affects as anxiety, depression and fatigue related to the thrombocytopenia and best hematological abnormalities as anemia (25). These symptoms adversely affect the health of the patients.

Depression during antiviral therapy

A correlation between depression and reduced tryptophan level in the patients taking IFN- α has been found (Schafer et al., 2009). On the other hand in most of the patients no depression affects have been found when IFNα are used in a low quantity. This reduces the burden of extra medications for depression to the Hepatitis patients (25). So, by knowing the risk of depression induced by IFNα, we can decide to pretreat the patient by a psychiatrist through psychotherapy. Physical symptoms occur at early stage of treatment, but depression symptoms are developed later (26)The major purpose of using interferon and ribavirin is to observe hematological changes because this reaction will tell us about the dysfunctioning mechanism of hematopoietic organs that allow anticipation and correction (27). Hemoglobin level lowers during treatment with interferon and ribavirin, which at the end of the treatment reaches at its lowest average value. Ribavirin causes anemia and additionally interferon inhibits the working of hematopoietic bone marrow. Anemia, in this case, does not have any compensatory reticulocytosis which confirms that there is no production of immature red blood cells in the bone marrow (28) In patients having condition of acute hepatitis and during therapy, blood examination reveal that there is a change in the morphology, shape and volume of the erythrocytes even in absence of anemic conditions (29). Almost 90% of patients having antiviral therapy expressed different levels of morphological changes in erythrocytes. This erythrocytes morphology tells us about the viral activity that is causing liver lesions progression and an infection of bone marrow. Microcytosis along with pancytopenia is caused due to insufficient hematopoiesis (in 25% cases) and 75% due to lack of blood cells in the bone marrow (hypoplasia) (30) Enlargement of red blood cells occurs due to metabolic disorders of folic acid and vitamin B12. This condition is observed in the patients suffering from chronic viral hepatitis and increased by interferon usage. In sixth month of treatment high value of MCV is observed

which comes to the normal level after six months of treatment discontinuation. Macrocytosis is expressed in both of the conditions; normoblastic marrow and megalobastic or bone marrow hypoplasia (31). In most of the cases, in patients taking formulation of interferon, a lowered value of cells is formed in the bone marrow with the high percentage of fibrous structure. All these affect are normalized after completion of the treatment especially in young patients having more bone regeneration ability than the older ones (32) Macrocytosis is considered a bad prognostic factor for progression of liver disease to cirrhosis. Anemia affects the efficacy and tolerability in addition with a poor quality of life and fatigue condition.

Anemia is the most important adverse hematological effect of ribavirin and interferon treatment that is observed from the first month of the therapy. Morphological change in erythrocytes due to bone marrow infection and liver lesion progression tells us about the viral activity. By the low quantity of reticulocytes and by lesser regeneration ability of bone marrow, the toxic effect of interferon is confirmed. If anemic condition reduces the hemoglobin level up to 20% then we should reduce the ribavirin dose for maintenance of patient's life (33).

Acute liver disease such as hepatitis C is very serious health issue that has many adverse hematological effects and serious effects on liver leading to cirrhosis (34). HCV infection has number of extra hepatic manifestation including non-Hodgkins lymphoma (B cell type) and mixed cryoglobulinemia. Patients infected with hepatitis C have non-hepatic malignancies increasingly. This phenomenon of HCV is unknown. HCV infection plays a key role in pathophysiology of lymph proliferative diseases (35). HCV can cause by B lymphocytes and infected lymphocytes in presence of HCV proteins could initiate dys-regulation growth and further molecular changes in the lymphocytes development leading to the malignant lymphoma (Turner et al., 2003). Inflammatory lesions in liver, progressive fibrosis of changing degrees and cirrhosis, steatosis, fibrosis and their consequences cause chronic hepatitis c virus (HCV) infections. Oxidative stress cause accumulation of DNA damage, chromosome stability to make the base for genomics for transformation of malignant hepatocyte. Here, we study epidemiology of HCC induced by HCV (36) HCV infection induces epigenetic changes that take part in hepatic carcinogenesis. Reactive oxygen species induced by HCV activate histone deacetylase enzyme in a fashion like hydrogen peroxide and cause hypo acetylation of histones. It has been shown that with the lack of methyl group from IGF 2 locus in hepatitis C cirrhosis causes hepatocellular carcinoma development (37)

Role of interleukins

When any pathogen enters the body, interleukins (IL-1 and IL-18) play very important role to fight with that pathogen in the result of inborn immunity. We want to know the effects of interleukins in presence of hepatitis C virus infection in hepatocytes or its induction with macrophages. When any pathogen related danger is found, inflammasomes (IL-1 activating platform) assemble in its response. There are special NOD like receptors on inflammosomes that intellect the viral protein or nucleic acid. When this is activated, a multiprotein complex is formed by NLRs which contain proteins related to apoptosis and caspase-1 for the assembly of inflammasomes (38). NLRP1, NLRP3, and NLRC4 sense the viral infection and activate the inflammasomes that further trigger pro inflammatory cytokines (IL18 and IL1). This production of IL1 and IL18 is a regulated by two signals of activation and release(39)The first signal activates NF-B synthesizes pro IL18 and pro IL1 messenger RNA in the Toll like receptor. In the second signal caspase-1 is activated which breaks the pro-IL-18 and pro-IL-1 into mature biologically active IL-18 and IL-1 (40) Pro-inflammatory cytokines (IL1 and IL6) and chemokine (IL8 and CCL2) has also an important role in hepatocytes and activated HSCs (41) In presence of IL6 and IL1 intrusive capacity of malignant cells increases (42). At the end we conclude that IL1 and IL18 are induced by the presence of HCV that further activates NF-B protein regulating pro inflammatory cytokines in

the macrophage ell line combating the HCV.

CONCLUSION

As Hepatitis C most commonly leads to the development of chronic liver diseases and hepatocellular carcinoma. There is strong need to find new strategies for its effective treatment and new research studies should be conducted for the development of new drugs to control this diseases globally.

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