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REVIWE ARTICLE

Brief Review on Combined Therapy of Sofosbuvir and Daclatasvir against Hepatitis C Virus

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ABSTRACT

Hepatitis C virus is a hepatotrophic, enveloped positive sense RNA virus belonging to the Hepacivirus genus and family Flaviviridae. Hepatocellular carcinoma (HCC), liver cirrhosis, and severe liver diseases are associated with hepatitis C virus (HCV) infections all over the world. According to the world health organization's annual report, around 71 million people worldwide are distressed with the virus, and approximately 400,000 of them pass away every year. HCV infection can be early diagnosed using serological assays. However, the delayed diagnosis may result in chronic infection, liver cirrhosis, liver cancer and death. There is no effective vaccine against hepatitis C. Because of the genetic diversity and complexity of HCV, only few treatments have been shown to be effective against all genotypes of the virus. Here, we review the current anti-HCV therapeutics such as direct acting antivirals (DAA) and discuss their mechanisms of action and drawbacks particularly Sofosbuvir and daclatasvir.

Introduction

Hepatitis C was discovered in 1987, Michael Houghton's team collaborating with Bradley's team in the Centers for Disease Control and Prevention, employed a novel molecular cloning approach to identify the unknown virus and develop a diagnostic test. Later In 1988, the confirmed virus was published. On other hand, transmission of hepatitis C virus via contaminated blood is responsible for most infections, these occurred by blood transfusion or drug injection; while in pregnancy, from mother to offspring occurs in fewer than 10% of pregnancies. Liver cirrhosis and hepatocellular carcinoma (HCC) are mostly caused by the hepatitis C virus (HCV). According to a recent estimate, 71 million people worldwide suffer from chronic hepatitis C virus infection, and one million new cases are reported each year [1]. WHO estimated that in 2022, approximately 242 000 people died from hepatitis C, mostly from cirrhosis and hepatocellular carcinoma (primary liver cancer). Over 95% of people with hepatitis C infection can be cured with direct-acting antiviral medications (DAAs), but diagnosis and therapy are not widely available. As of right now, there is no reliable vaccine to prevent hepatitis C [1]. There are twelve million persons chronically affected in the Eastern Mediterranean Region which has the

largest disease burden. People with chronic HCV infections are found in the Western Pacific Region (7 million), the European Region (9 million), and the South-East Asia Region (9 million). Five million persons in the Americas and eight million in Africa are chronically infected [1]. The most infected individuals live in middle income countries [2]. Collectively, China, Pakistan, Nigeria, Egypt, India, and Russia were responsible for over 50% of all infections [3]. HCV is a single-stranded, positive-sense flavivirus that is a member of the *Amarillovirales* order, *Flaviviridae* family, and *Hepacivirus* genus. HCV is an RNA virus with a genome of about 9.6 kb. A single open reading frame (ORF) in its genome codes for 3011 polypeptides with amino acids [4]. Host and viral proteases degrade the HCV polyprotein into three structural proteins (Core, E1, and E2) and seven non-structural proteins (P7, NS2, NS3, NS4A, NS4B, NS5A, and NS5B) [5]. Viral nucleotides essential to viral pathogenesis are produced by HCV-core, while E1 and E2 proteins facilitate the entrance of viruses into cells [6]. The P7 aids in the assembly and release of the HCV virus as well as the translocation of NS2 into the endoplasmic reticulum [7]. One transmembrane protein involved in viral replication is the NS2 peptide. Protease NS3 also functions as an ATPase and helicase [8]. NS4A is a cofactor for NS3 protease, and NS4B and NS5A participate in viral replication to recruit other viral proteins [9]. The non-structural protein, also known as NS5B, is an RNA polymerase (RdRp) involved in RNA replication that is reliant on HCV [10]. The prevalence of hepatitis C virus (HCV) genotypes varies between nations [3]. Globally, genotype 1 HCV is the most common (49.1%), followed by genotype 3 (17.9%), genotype 4 (16.8%), and genotype 2 (11%). With 17 recognized subtypes, genotype 4 (GT4) is genetically heterogeneous and accounts for around 13% of infections globally. The Middle East and North Africa have the highest percentages of GT4 (71%) [3]. Ever since HCV infection first appeared, Egypt has struggled with this public health issue. Following schistosomiasis, it assumed the burden of liver disease.

The diagnosis of HCV infection is as follows: a) Using a serological test to check for anti-HCV antibodies, individuals who have contracted the virus are identified. b) In order to confirm a chronic infection and the necessity of treatment, a nucleic acid test for HCV ribonucleic acid (RNA) is required if the test results for anti-HCV antibodies are positive. c) Cutting-edge novel tests, like the HCV core antigen, are being developed for diagnostics and will eventually allow for a one-step diagnosis of an active hepatitis C infection [1]. In Egypt, approximately 93% of HCV infections are genotype 4 (G4), with subtype 4a being the most common [11]. The virus is able to elude the host immune system as well as conventional antiviral treatments due to the continuing evolution of the HCV quasispecies [12]. Moreover, there isn't a vaccine that can shield against HCV [13].

Treatment with pan-genotypic direct-acting antivirals (DAAs) is advised by WHO for all adult patients suffering from chronic hepatitis C infection. The short-term, oral DAA therapy regimens are curative and rarely cause negative effects. Most people with HCV infection can be cured with DAAs, and treatment only takes a short while (typically 12 to 24 weeks), depending on whether cirrhosis is present or not [1]. Chemotherapeutic intervention may be used to target certain viral activities that are part of the replicative cycle of an infected cell [14]. Many compounds, both nucleosides and non-nucleosides, have currently been developed that interact with viral targets to stop viruses from spreading [15]. The only known HCV treatment plan was the traditional one, which involved 24–48

weeks of Peg-interferon (PEG-IFN) alfa, ribavirin (RBV), and either 2a or 2b depending on the genotype of the virus until 2011[16]. However, the therapy has some disadvantages, such as a low sustained viral remission (SVR), a lengthy course of treatment, and severe side effects, particularly in genotype 4 [17]. Since 2015و new direct-acting antiviral drugs (DAAs) has been developed for the treatment of chronic HCV. These medicines have very high rates of SVRs, in which HCV RNA is undetectable 12 or 24 weeks after treatment ends. They are safe, effective, well-tolerated, and short-term therapies [18]. Since the beginning of 2016, the National Committee for Control of Viral Hepatitis (NCCVH) has altered the national guidelines for treating HCV patients to only include IFN-free treatment, which involves giving Sofosbuvir/ Daclatasvir with or without ribavirin for a 12-week period. This modification was made possible by the drug's low cost, short duration of well-tolerated regimens, high rates of SVR12, fewer side effects, and demonstrated efficacy and safety in patients with chronic HCV [19]. The viral proteins involved in viral replication were the focus of these medications [20]. Together with daclatasvir (DCV), a powerful, pan-genotypic inhibitor of the HCV NS5A protein, NCCVH has approved sofosbuvir, a nucleotide analogue HCV NS5B polymerase inhibitor that binds to the NS5B RNA-dependent RNA polymerase and prevents viral replication, as an effective HCV treatment with SVR rates approaching 95% [21]. In an effort to eradicate the disease, Egypt initiated the largest mass screening and treatment program for HCV infection in late 2018; it has the capacity to screen 50 million individuals [22]. Over the past ten years, Egypt has persisted in managing its HCV infection and is striving to achieve the WHO's global goal of eradicating viral hepatitis. A major shift in HCV management occurred because of the development of DAAs, which made treatment accessible to everybody [23]. Worldwide, 12-week antiviral treatment regimens, including as Sofosbuvir/ Velpatasvir, Sofosbuvir/ Ledipasvir, and Sofosbuvir/ Daclatasvir, were used with the goal of targeting NS3-4A protease, NS5A region, and NS5B polymerase [24]. Even though DAAs have a high SVR rate of 90–95%, 5–10% of patients still fail to completely eradicate HCV infection [25]. Resistance-associated substitutions (RASs) are polymorphisms found in the viral loci (NS3-4A, NS5A, and NS5B) that DAAs target, and their existence has been linked to treatment failures [26]. RASs are produced both at baseline and in individuals with chronic hepatitis C patients who do not improve with DAA therapy. Since NS5A and NS5B inhibitors are included in all DAA regimens now available, RAS in NS5A and NS5B may affect the efficacy of re-treatment [27]. As of right now, Daclatasvir is the only NS5A inhibitor approved for use in treating individuals with HCV-4 infection who have widespread cross resistance in addition to a low genetic barrier to resistance [28]. Sofosbuvir is also the only NS5B nucleoside inhibitor that possesses a robust genetic barrier to resistance, a respectable safety record, and is readily available for purchase. For this reason, it is used in Egypt in conjunction with NS5A inhibitors to form all-oral interferon-free regimens for the treatment of HCV-4 infection [19]. The current study provides an update on chemotherapeutic medications that target different phases of the HCV viral life cycle and infected host cell functions that can be interfered with to prevent viral multiplication and the subsequent series of detrimental effects.

Sofosbuvir and Daclatasvir: dosage, mode of action, side effect

The Egyptian National Committee for the Control of Viral Hepatitis launched a nationwide mass treatment effort to

eradicate HCV in Egypt following the discovery of extremely successful DAA therapy. Direct Acting Antivirals was created to combat a vital route specific to the viral life cycle. Protease NS5a inhibitors, NS5B polymerase inhibitors, and NS3/4 protease inhibitors are antiviral medicines. Two strategies have been used in antiviral therapy to suppress HCV RdRp. Non-nucleoside inhibitors (NNIs) that alter the binding of the enzyme to the substrate by interacting with RdRp distant from the active site [29] and as the entering nucleotide triphosphate competes with nucleotide inhibitors (NIs) for binding and inclusion into the expanding polypeptide chain [30]. DAAs function by blocking certain HCV non-structural proteins (NS), which are essential for the virus's reproduction. Inhibitors of NS3/4A include boceprevir, telaprevir, simeprevir, asunaprevir, grazoprevir, and paritaprevir. As well as examples of NS5A inhibitors include velpatasvir, elbasvir, daclatasvir, ledipasvir, and ombitasvir. In addition to examples of NS5B inhibitors are dasabuvir and sofosbuvir (**Figure 1**).

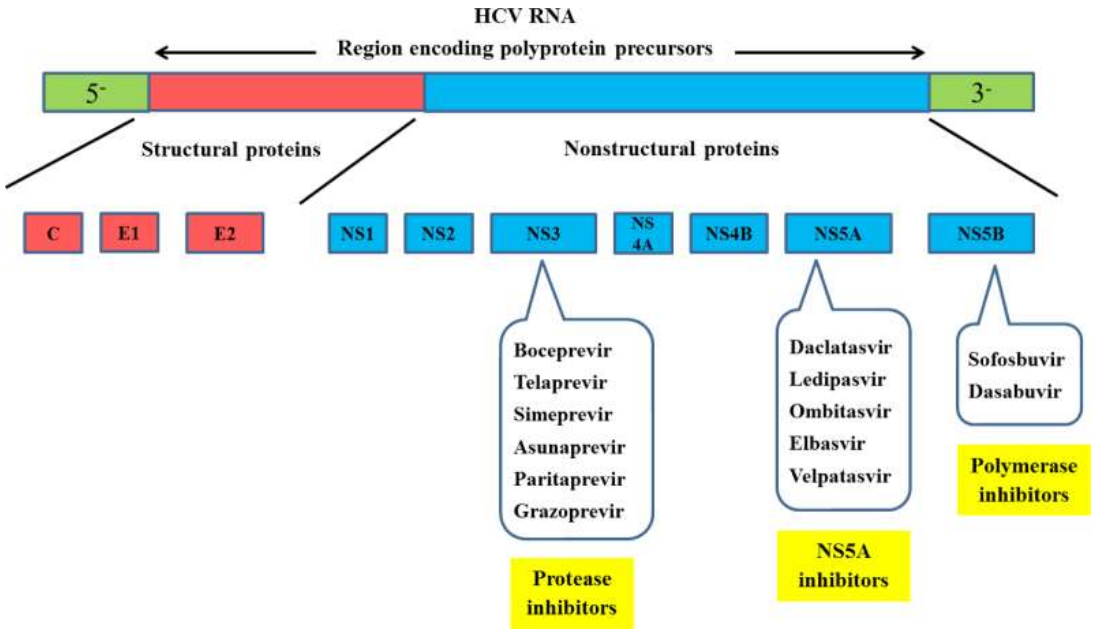

Figure 1: Hepatitis C virus-encoded proteins as targets for direct acting antiviral drugs Geddawy et al.[18].

The current standard of care for HCV infections involves combining two or more DAAs. But several obstacles are keeping DAA therapy from working as well as it should, including the possibility of drug-drug interactions and resistant mutation. Another clinical problem with DAA is the absence of pertinent clinical pharmacology data and knowledge about medication interactions. A major breakthrough was made in 2013 with the approval of sofosbuvir (SOF), a second-generation DAA and NS5B polymerase inhibitor. Improved pharmacokinetics and resistance profiles are two aspects of sofosbuvir's pan-genotypic impact on HCV [31]. DAAs based on sofosbuvir are safe, efficacious, and well tolerated in patients with chronic hepatitis C [32].

The most powerful and adaptable medication is SOVALDI (sofosbuvir) [33], which has demonstrated increased effectiveness when combined with PEG-IFN and other DAA. When taken orally, it

has been demonstrated to have a high therapeutic potency and resistance barrier. By mimicking a nucleotide and blocking the viral NS5B, SOF prevents HCV replication [34]. Because of its effectiveness against a wide range of genotypes, it can be provided without the need for concomitant interferon. Patients with genotypes 1-4 respond well to DAKLINZA ("a combination of sofosbuvir and Daclatasvir"), either with or without ribavirin [35]. As part of a combination antiviral medication regimen, sofosbuvir (SOF), a pyrimidine nucleotide analog inhibitor of NS5B, is recommended for the treatment of HCV genotypes 1a, 1b, 2, 3, and 4. [36]. Within the cell, sofosbuvir phosphorylates, binds to the expanding viral RNA strand, and stops the HCV RNA strand from extending to its maximum length [37]. When used as a monotherapy, Sofosbuvir has a strong genetic barrier against resistance; in several clinical trials, resistance has only been detected in one patient [38]. Sofosbuvir has demonstrated promise in treating people with genotypes 1-6 when paired with peg-IFN and RBV [39]. It has been demonstrated that SOF is a great substitute for IFN in patients who cannot benefit from IFN therapy or who have quit IFN due to side effects [40]. When SOF was administered with IFN or for a longer treatment period (24 vs. 12 weeks), the most frequent adverse effects were noted. RBV was also one of the side effects in phase 3 trials when it was administered with RBV. The adverse effects were chills, pyrexia, myalgia, influenza-like symptoms, decreased appetite, and neutropenia when coupled with RBV and IFN [41]. At a dosage of once daily, sofosbuvir is another pangenotypic oral NS5B inhibitor that is both safe and efficacious. Few medications interact with it. Patients with genotypes 1 or 4, which are thought to be difficult to treat, showed a high rate of SVR when daclatasvir and sofosbuvir were combined. Patients with cirrhosis who have received prior treatment have a higher SVR rate when ribavirin is added [42]. The American Association for the Study of Liver Diseases (AASLD) and the Infectious Diseases Society of America (IDSA) jointly approved sofosbuvir as first line therapy for all six genotypes of HCV [43]. Following 12 weeks of daily treatment, sofosbuvir is frequently used in conjunction with other antivirals to generate a sustained virologic response (SVR) or cure, depending on the genotype. Possible combinations include Ledipasvir, Velpatasvir, Daclatasvir, Simeprevir, Elbasvir, Grazoprevir, Ribavirin, Peginterferon alfa-2a, or Peginterferon alfa-2b. Significant long-term health advantages are linked to SVR and HCV eradication, including as decreased liver-related damage, enhanced quality of life, decreased hepatocellular carcinoma incidence, and decreased all-cause mortality [44]. The most common side effects of treatment with direct acting antivirals, including sofosbuvir, are headache and fatigue. Compared to earlier interferon- and ribavirin-based regimens that were constrained by infusion site reactions, decreased blood count, and neuropsychiatric issues. The lack of significant side effects and brief medication duration is a significant benefit [16]. Patients with chronic HCV infection who have HCV genotypes 1-6 or who are co-infected with HIV are treated with sofosbuvir in combination therapy with other antiviral drugs. But the NS5B substitution mutation S282T has been linked to decreased sensitivity to sofosbuvir [45]. HCV NS5B (non-structural protein 5B) RNA-dependent RNA polymerase is particularly inhibited by the nucleotide analog inhibitor sofosbuvir. After going through intracellular metabolism, sofosbuvir uses NS5B polymerase to incorporate into HCV RNA and form the pharmacologically active uridine analog triphosphate (GS-461203), e polymerase, which stops new HCV genetic material

from being replicated [46]. Daclatasvir is a direct-acting antiviral medication used to treat chronic infections caused by HCV genotypes 1 and 3. It is marketed as hydrochloride salt as daily oral tablets under the brand name DAKLINZA [43]. The first medication to treat HCV genotype 3 with proven safety and therapeutic efficacy that didn't require ribavirin or interferon co-administration was daclatasvir by attaching itself to NS5A, a nonstructural phosphoprotein generated by HCV that prevents RNA replication and virion assembly; it exerts its antiviral effect. The D1 domain of NS5A cannot interact with host cell proteins and membranes when it is connected to the domain's N-terminus, which is crucial for the virion replication complex's assembly. Daclatasvir has been demonstrated to target the Tran- and cis-acting properties of NS5A. By altering the phosphorylation state of NS5A, it also disrupts the activity of newly formed HCV replication complexes [47]. Positions Q30 (Q30H/K/R) and M28 were the most common critical NS5A amino acid alterations that decreased sensitivity to daclatasvir therapy in individuals with genotype 1a; position Y93H was the most common mutation in people with genotype 3. For genotype 1a/b individuals with or without cirrhosis, the 2017 American Association for the Study of Liver Diseases (AASLD) guidelines suggests 60 mg of daclatasvir in addition to 400 mg of sofosbuvir as second-line therapy. For patients with genotype 3 who do not have compensated cirrhosis, the same dosage schedule can be used as first-line therapy; for those who do, it can be used as second-line therapy. Patients who are difficult to treat because of severe cirrhosis, post-liver transplant HCV recurrence, or HIV-1 coinfection can benefit from combination therapy that uses daclatasvir. After 12 weeks of daily therapy, the goal of treatment is to either cure the patient or cause a sustained virologic response (SVR12). Significant long-term health benefits, including as decreased liver-related damage, enhanced quality of life, a lower incidence of hepatocellular carcinoma, and a drop in all-cause mortality, are linked to SVR and HCV eradication [44]. In July 2015, the FDA authorized daclatasvir to treat HCV genotype 1 and 3 infections when used with or without ribavirin and sofosbuvir (Sovaldi). Patients with cirrhosis and HCV genotype 1a infection who were taking daclatasvir and sofosbuvir as treatment-naïve had SVR12 values of 88% and 99%, respectively. In patients who had never had treatment and had HCV genotype 3 infections with or without cirrhosis, the identical dosage schedule produced 71% and 98% SVR12 rates, respectively. Daclatasvir inhibits both viral RNA replication and virion assembly by binding to the N-terminus of NS5A and causing structural distortions that hinder NS5A activities. Absorption and bioavailability: 60 mg of daclatasvir is administered orally once a day. When taken orally, daclatasvir is well absorbed, reaching peak plasma concentrations two hours after dosage; when compared to fasting conditions, a high-fat diet reduces daclatasvir bioavailability. A typical diet has no effect on the bioavailability of daclatasvir [48]. The pharmacokinetic profile of daclatasvir, an NS5A inhibitor, permits pangenotypic effectiveness against the six major HCV genotypes and a once-daily dosing. Daclatasvir is physiologically benign. Headache is the most common adverse event to occur. Since daclatasvir is a weak cytochrome P450 inducer, there aren't many drug interactions with it. By attaching to the N-terminus of NS5A and resulting in structural alterations that impair NS5A functions, daclatasvir prevents viral RNA replication as well as virion assembly. Both bioavailability and absorption: Once day, 60 mg of daclatasvir is taken orally. A high-fat diet lowers daclatasvir bioavailability when compared to fasting settings; when taken orally, daclatasvir is

effectively absorbed and reaches peak plasma concentrations two hours after dosing. The bioavailability of daclatasvir is unaffected by a normal diet [48]. The NS5A inhibitor daclatasvir's pharmacokinetic characteristics allows for once-daily dosage and pangenotypic efficacy against the six main HCV genotypes. Daclatasvir has no negative physiological effects. The most frequent adverse event is a headache. Daclatasvir has few medication interactions because it is a poor cytochrome P450 inducer. Furthermore, because its primary metabolism is hepatic, people with chronic kidney disease can utilize it without changing their dosage. In addition to other DAAs, Daclatasvir at the prescribed dosage is advised to prevent the development of resistant infections [43]. Resistance: Individuals with genotypes 1a, 1b, and 3a have been linked to reduced susceptibility to daclatasvir due to polymorphisms at NS5A amino acid positions M28, Q30, L31, and Y93. Because they are more likely to develop resistance, patients with cirrhosis and HCV genotype 1a are advised to have NS5A Resistance Testing done before starting treatment. Mechanism of action: The functional replication complex, which includes the viral nonstructural phosphoprotein NS5A, causes the viral RNA genome to be amplified on endoplasmic reticulum membranes. It is capable of adhering to HCV RNA. Depending on its phosphorylation state, it has been demonstrated to have two different roles in HCV RNA replication. Basally phosphorylated NS5A mediates the maintenance of the HCV replication complex, whereas hyperphosphorylated NS5A has a trans-acting function that regulates HCV assembly and the production of infectious particles [47]. Daclatasvir has been demonstrated to hyperphosphorylated NS5A proteins, impairing the ability of recently created HCV replication complexes to operate. Moreover, daclatasvir has been shown to inhibit not only virion assembly and secretion in vivo, but also the synthesis of intracellular viral RNA [49]. RBV is advised for all HCV genotypes according to consensus guidelines from the Canadian Association for the Study of the Liver (CASL, 2015) and the American Association for the Study of Liver Diseases (AASLD, 2017). Ribavirin monotherapy is always used in conjunction with other treatments to treat HCV infections since it cannot produce a sustained viral response. [50]. Interferon and ribavirin are frequently given together in regimens; this is known as triple combination therapy and is frequently authorized [51]. Protease inhibitors, when used in conjunction with normal IFN/RBV treatment, can increase the rate of SVR in naive genotype 1 patients by around 70% [51]. Peg-IFN and ribavirin treatment are utilized in combination with two first-generation protease inhibitor DAAs, VICTRELIS (boceprevir) [52] and INCIVEK (telaprevir) [53]. Because it may activate IFN-stimulated genes, which create proteins that block multiple stages of viral replication, IFN-alfa has strong antiviral action [54].

Furthermore, IFN-alfa interacts with the host's innate and adaptive immune responses in an immunomodulatory manner. IFN-alfa stimulates T-helper cell growth in T lymphocytes rather than Th2 cells, leading to an upsurge in interleukin (IL)-2 and IFN-gamma production. Furthermore, IFN-alfa reduces inflammation by blocking the synthesis of several cytokines, such as IL-1 and tumor necrosis factor (TNF) [53]. Ribavirin is a guanosine analogue that was found in 1972 by Witkowski and colleagues [54]. Interferon and ribavirin are frequently given together in regimens; this is known as triple combination therapy and is frequently authorized [51]. Protease inhibitors, when used in conjunction with normal IFN/RBV treatment, can increase

the rate of SVR in naive genotype 1 patients by around 70% [51]. Peg-IFN and ribavirin treatment are utilized in combination with two first-generation protease inhibitor DAAs, VICTRELIS (boceprevir) [52] and INCIVEK (telaprevir) [53]. Because it may activate IFN-stimulated genes, which create proteins that block multiple stages of viral replication, IFN-alfa has strong antiviral action [54]. It exhibits wide-ranging effects on a variety of DNA and RNA viruses. Although ribavirin was initially approved to treat only severe respiratory syncytial virus (RSV) infections in children, it has now been used to treat a number of viruses, including Lassa fever virus infection and influenza A and B [55]. Research on ribavirin treatment for HCV was underway in the early 1990s. Despite improvements in liver histology and serum aminotransferase levels [56]. Ribavirin alone itself did not significantly change HCV RNA levels [57]. No further benefit in terms of virologic clearance was observed when the drug was continued [58]. Thus, ribavirin has only been used in conjunction with IFN-alfa to treat chronic HCV. According to these clinical results, people might not get the complete or instantaneous suppression of viral replication that ribavirin by itself can offer [59]. Due to a lack of effective HCV culture methods and animal models, it has been difficult to comprehend the molecular mechanisms behind ribavirin's antiviral action against HCV. Based on findings from research on other RNA viruses and the scant knowledge on HCV, there are four possible mechanisms for ribavirin's antiviral efficacy when used alone: Four tactics are used to stop a rapidly spreading virus from reaching the point of catastrophic catastrophe: HCV replication is directly inhibited; the host enzyme inosine monophosphate dehydrogenase (IMPDH) is inhibited; mutagenesis is induced; and a Th1 immune response is developed to modulate the immune system. Ribavirin enhances the clinical setting's ability to prevent relapses once medication stops. In comparison to patients treated with pegylated IFN-alfa alone, Hermann and colleagues observed a quicker decrease in viral load in the third phase of therapy (after Day 28) in patients treated with pegylated IFN-alfa and ribavirin combination therapy [60]. Compared to genotypes 2 and 3, a longer course of treatment and a higher dose of ribavirin are needed to effectively treat genotype 1 HCV infection. It has been shown that genotype 1 infected individual with high viral loads can develop SVR when given large doses of ribavirin (mean of 2,500 mg daily) [61]. According to these findings, patients infected with genotype 1 often do not respond to interferon (IFN); nevertheless, elevated ribavirin levels may be able to reverse this effect. Therefore, ribavirin seems to be less susceptible than IFN-alfa to changes in HCV genotype [62].

Conclusion

WHO has stated that it will be feasible to eradicate HCV by 2030. Even though there are a lot of medicines available, none are without adverse effects, and in low-income nations, many treatments are still highly expensive as well as DAAs do not shield users from reinfection. Furthermore, the usage of these antiviral medications will cause resistant strains of the virus to arise, which will increase the number of HCV-infected individuals in the future. To further comprehend and create pan-genotypic medicines, more study on genotype-specific variations and similarities is required.

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الملخص العربي

مراجعة مختصرة حول العلاج المشترك للسوفوسبوفير والداكلاتافير ضد فيروس التهاب الكبد الوبائي

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فيروس إلتهاب الكبد الوبائي سي هو فيروس RNA مغلف ينتمي إلى جنس الفيروسات الكبدية وعائلة الفيروسات المصفرة. يرتبط سرطان الخلايا الكبدية وتليف الكبد وأمراض الكبد الوخيمة بعدوى فيروس إلتهاب الكبد الوبائي في جميع أنحاء العالم. ووفقا للتقرير السنوي لمنظمة الصحة العالمية، يصاب حوالي 71 مليون شخص في جميع أنحاء العالم بهذا الفيروس، ويتوفى ما يقرب من 400 ألف منهم كل عام. يمكن تشخيص الإصابة بفيروس إلتهاب الكبد الوبائي (HCV) مبكرًا باستخدام الاختبارات المصلية حيث ان التشخيص المتأخر قد يؤدي إلى عدوى مزمنة وتليف الكبد وسرطان الكبد والوفاة. لا يوجد لقاح فعال ضد إلتهاب الكبد الوبائي سي بسبب التنوع الجيني والتعقيد المركب للفيروس حتى الان ، وأيضا لم يثبت سوى عدد قليل من العلاجات فعاليتها ضد جميع الأنماط الجينية للفيروس.لذلك قامت هذه الورقة البحثية بمراجعة العلاجات الحالية المضادة لفيروس إلتهاب الكبد الوبائي سى مثل مضادات الفيروسات ذات التأثير المباشر (DAA) وناقشت آليات عملها المعروفة وعيوبها مع التركيز على تلك العلاجات (سوفوسبوفير وداكلاتاسفير) بالأخص.