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Direct-acting antiviral agents (DAA) in the management of hepatitis C in a clinical setting: Effectiveness and limitations

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Abstract. Hepatitis C virus (HCV) significantly burdens public healthcare resources and has infected over 73 million people as of 2023. Past treatments for hepatitis C virus relied on ribavirin pegylated interferon. However, this treatment has adverse side effects, such as depression, anemia, etc. At the same time, this method has a low cure rate and poor patient compliance. DAA can not only treat CHC and even cirrhosis, but also play a crucial role in mediating the recovery of immune damage and regulating glucose metabolism in infected patients. In the contemporary approach of HCV, Direct-acting antiviral agents (DAA) resulted in up to 90% cure rates. At the same time, clinical trials showed DAA also provides many benefits to patients during treatment. Still, with the widespread use of DAA, some DAA limitations have also been identified during its use. This article summarizes the benefits and limitations that DAA has demonstrated in the current treatment of HCV.

Keywords: Hepatitis C Virus (HCV), Direct-Acting Antiviral (DAA), Sustained Viral Response (SVR).

1. Introduction

Globally, HCV infection and its aftereffects have significantly strained the world's public health and social services. As of 2023, WHO estimates that 0.73 billion individuals are globally afflicted with HCV [1]. Additionally, 1.5 million people are thought to get newly infected with HCV each year, with a prevalence rate of 2.5% [2]. HCV Infection was the primary reason of CHC, which affects an estimated 58 million individuals worldwide, including 3.2 million children and adolescents [1]. HCV is a liver disease with a well-defined mode of transmission and a high degree of chronicity, with approximately 20-30% of individuals with persistent HCV infection experiencing progression to cirrhosis [3]. In comparison, about 4% cirrhotic HCV-infected patients have a high risk to develop hepatocellular carcinoma and 2% to 5% those to develop end-stage liver disease [3].

HCV is a highly variable infectious agent that can be categorized into 100 subtypes based on its seven genotypes (GT). It is acknowledged that there are regional variations in the global distribution of HCV genotypes, with GT1 (46.2%) and GT3 (30.1%) dominating global infections; HCV genotypes 2, 4, and 6 collectively contribute to around 22.8% of infections. Additionally, the proportions of getting GT7 infections are also tiny, and to date, GT7 infections have only been found in a minimal number of patients.

HCV clearance with SVR has been designated the benchmark for measuring HCV cure in all significant international guidelines. For the past 20 years, HCV has been treated with continuous

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administration of pegylated-interferon with ribavirin (PegIFN/RBV) administered for a duration ranging from 24 to 72 weeks to achieve an SVR. However, this treatment has apparent drawbacks, such as low SVR, low cure rates, prolonged treatment times, significant adverse effects, poor patient compliance, etc. Statistics show that a tiny proportion of patients who use the medication can obtain a high SVR, resulting in a low cure rate. Meanwhile, multiple adverse effects, such as depression, cytotoxicity, and hemolytic anemia, have been reported in more than 10% of patients after completion of treatment [4]. However, as DAA medications are advocated for the management of diverse genotypes and subtypes of HCV infections, clinical studies have indicated that DAA therapy is an effective method of treating CHC, and even liver cirrhosis, by inducing a high SVR with fewer adverse effects after treatment [4].

DAA is not only an effective treatment for HCV. Still, clinical trials have also shown that it plays a vital role in mediating recovery from immune damage and regulating glucose metabolism in infected patients. However, there are still many limitations regarding the clinical use of ADD, including the potential for drug resistance post-DAA treatment, the generic DAA safety, and the impact of concurrent intake of multiple drugs on DAA efficacy. This article will focus on DAA's current effectiveness and limitations in clinical use.

2. DAA mechanism of action in detail

DAA medications are also recognized as STAT-C drugs. Depending on the specific mechanism of action of DAA drugs, they can be subdivided into NS3/4A protein-lowering inhibitors, nucleoside and non-nucleoside inhibitors of NS5B polymerase, and inhibitors of NS5A protein, which are integral components of the antiviral arsenal against HCV [3].

2.1. NS3/4A protease inhibitor

The innate immune system utilizes TLR to detect specific PAMP across a broad spectrum of microbes. TLR is crucial for quickly activating type I interferon (Type 1 IFN). In this scenario, TLR signals trigger the production IRF-3 by recruiting particular adaptor molecules. IRF-3 then triggers the production of IFN-β, which boosts the type 1 IFN response and produces antiviral activity, activating the innate immune system to aid in the defense against HCV infections. However, studies of HCV over the last decade have shown that levels of the NS3/4A protease elevate in individuals afflicted by HCV infection, and experiments have found that NS3/4A protease causes specific protein proteolysis of TLR domain-containing adaptor (Domain-containing adaptor is in charge of connecting the TLR3 to the kinase responsible for the activation of IRF-3) [5]. That proteolysis of the signaling pathway would inhibit IRF-3 activation, thus possibly inhibiting the expression of the type 1 IFN that restricts viral replication [5]. In addition, HCV-induced impaired expression of type 1 IFN and other cytokines may inhibit or delay the elimination of HCV by adaptive CD8+ T cells. This mechanism of immune evasion restricts the expression of the patient's defense genes, leading to persistent HCV infection.

However, this challenge has been effectively addressed by successfully creating NS3/4A protease inhibitors. These inhibitors represent the pioneering approach to impeding the proteolysis process associated with NS3/4A protease. This advancement has demonstrated its potential to effectively eliminate HCV by facilitating the expression of IFN after the activation of IRF-3. This, in turn, triggers the patient's innate immune system response, reducing HCV replication and ultimately attaining SVR. When combined with an NS5A inhibitor, third-generation, pan-genotypic NS3/4A protease inhibitors showcase robust antiviral activity, boasting cure rates surpassing 95%. This notable achievement underscores their potency [6].

2.2. NS5B polymerase inhibitor

NS5B functions as an HCV RdRp, assuming a pivotal role in synthesizing HCV RNA within the patient [7]. In vitro experiments using recombinant RdRp have shown that the enzyme has two biochemical activities. First, the enzyme can catalyze RNA synthesis primer-dependently, extending from the 3-terminal end of the RNA molecule. At the same time, RdRp from HCV is also able to

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catalyze transcription from scratch in a primer-independent mechanism, in which the polymerase catalyzes the formation of a dinucleotide molecule at the 3-terminal end of the template, which can then be used as a primer for replication [8]. This mechanism is harmless to the viral genome, resulting in the entire genome being replicated from start to finish, and these two modes of activity of RdRp then appropriately explain the mechanism by which the NS5B polymerase efficiently replicates HCV RNA in vivo and the difficulty in curing the infection in HCV patients. Nevertheless, this challenge has been primarily addressed through the successful development of NS5B polymerase inhibitors, which was categorized into nucleoside and non-nucleoside inhibitors targeting the NS5B polymerase [7].

Clinical investigations have revealed that Nucleoside inhibitors (NI) are analogs of nucleosides integrated into the developing genome by the RdRp. This integration obstructs the further incorporation of incoming nucleotides. On the other hand, non-nucleoside inhibitors (NNI) are a class of RdRp inhibitors that operate unrelated to the nucleotide substrate. Instead, these compounds attach to the RdRp and obstruct the essential conformational changes required for polymerase activity [7]. The combined usage of NS5B polymerase and protease inhibitors has exhibited compelling outcomes in clinical trials. Notably, 100% of patients with G1 infection gained sustained virological response 4 weeks after treatment (SVR4). This achievement once again underscores the effectiveness of NS5B polymerase inhibitors.

2.3. NS5A protein inhibitor

HCV RNA replication is catalyzed by NS5A proteins, which also significantly promote fast HCV RNA replication. Non-structural NS5A proteins perform various diverse tasks, such as helping viruses replicate, assemble, and interact intricately with cellular processes. The former describes the direct interaction between NS5A and RdRp in vivo and in vitro that promotes the creation of negative RNA strands catalyzed by RdRp. The latter, on the other hand, involves NS5A proteins' prevention of apoptosis and stimulation of carcinogenesis, both of which may contribute to the process that results in a challenging treatment for HCV or even its development into hepatocellular carcinoma. The development of NS5A protein inhibitors, which have been demonstrated to prevent the replication of the RNA genome and the assembly of viral particles, can, however, successfully solve this issue. The NS5A protein's capacity to control HCV replication inside the replication complex is blocked by its binding to the protein's structural domain I [9]. It cannot successfully catalyze RNA for replication due to interrupting replication complex assembly.

Furthermore, NS5A inhibitors possess the capability to halt the assembly and discharge of viral particles by redirecting NS5A proteins to incorrect cellular locations within infected cells. This dual-action mechanism empowers patients to effectively eradicate HCV subsequent to drug administration, positioning NS5A inhibitors as the foundational components in combinations of anti-HCV drugs [9]. Clinical investigations have illuminated the potency of NS5A protein inhibitors in combination with other categories of DAA. These combinations have exhibited remarkable success rates in clinical trials, with over 90% of patients achieving sustained virological response (SVR). This resounding achievement showcases the effectiveness of NS5A inhibitors in curing HCV patients [10].

3. Current EFFECTIVENESS of DAA use in the treatment of HCV

3.1. Rehabilitation of immune damage

Clinical trials have substantiated the advantageous role of DAA therapies in achieving SVR for patients, consequently enhancing their immune systems following successful treatment for HCV infection. Research indicates that HCV-specific CD4+ T cells involved in upholding the response of CD8+ T cell, thwarting the virus from circumventing the T cell response. The inefficiency of CD8+ T cell response to virus stems from the absence or insufficiency of CD4+ T cell paracrine activity [11]. Diverse degrees of functional impairment are observed in the effector function of HCV-specific T cells, resulted in viral persistence due to ongoing exposure to viral antigens and varied immunological

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factors during CHC infection. Notably, Spanish researchers have highlighted the potential of DAA therapy in restoring the function of those cells. In a study involving 27 patients with CHC infection treated using DAA in a tertiary care hospital, the study revealed that in most HCV elimination through DAA treatment, the proliferation of HCV-specific T cells exhibited significant enhancement. This effectively illustrates the restoration of HCV-induced compromised immune responses following DAA administration [11].

Moreover, the research conducted by Shikha Shrivastava and colleagues unveiled a decline in the proportion of phenotypically exhausted T cells and a reduction in the expression of markers associated with T cell depletion during DAA treatment. Remarkably, there was a concurrent rise in the percentage of HCV-specific CD8+ cells. Following successful treatment, the expression levels of cytokines were elevated compared to baseline levels, indicating a partial restoration of immune reaction [12]. Additionally, a consistent increase in regulatory T cells was observed in patients four years after the clearance of HCV infection with DAA therapy, which suggests that DAA treatments exert a prolonged positive influence on liver immune function long after the elimination of HCV. In summary, effective DAA therapy can reinstate the immune impairment caused by HCV infection in patients, resulting in decreased depleted T cells and an increasing of those CD8+ cell responses. Furthermore, DAA treatment's enduring impact on liver immune function restoration is evident post-successful therapy [12].

3.2. DAA drugs impact glucose metabolism

Clinical trials have demonstrated the substantial impact of DAA therapy on enhancing glycemic control in patients with hepatitis C and T2DM after completing the treatment regimen. T2DM falls within the category of prevalent extra-hepatic disorders characterized by elevated blood glucose levels, increased thirst, frequent urination, fatigue, and lack of energy. Concurrently, research exploring the correlation between HCV and T2DM has examined 370 patients with liver infections; this study revealed T2DM patients having an obviously high risk of HCV-infected than other liver infections, underscoring the link between T2DM and HCV [13]. Clinical investigations have uncovered that DAA therapy can profoundly enhance glycemic control over the long term, following comprehensive monitoring and study of these patients. Significant reductions in fasting blood glucose and HbA1c were founded in 370 patients accepting SVR and did not experience a relapse within the initial four weeks of DAA treatment. Importantly, these reductions persisted even after the conclusion of the treatment regimen [13]. An Egyptian researcher validated this hypothesis through an experiment involving 400 patients treated with DAA therapy alongside 60 patients who did not receive DAA treatment. Among the 378 patients who achieved SVR, the author noted an enhancement in glycemic level in about 77% of patients with HCV and T2DM. These findings robustly support the assertion that an elevated likelihood of T2DM development exists after HCV infection. Moreover, DAA therapy, as a treatment modality, not only facilitates successful cure and attainment of SVR but also contributes to the enhancement of glycemic control, leading to reductions in glucose and HbA1c among patients with HCV and T2DM [14].

4. Current Limitations of DAA use in the treatment of HCV

4.1. The potential for drug resistance after DAA treatment

However, DAA has a high SVR for HCV patients, there are challenges of drug resistance, particularly resistance-associated substitutions (RASs) leading to failure of treatment. Due to HCV's strong adaptability and inability to maintain a sufficient level of inhibition, drug resistance is a natural and unavoidable problem, and it will decrease the cure rate [3]. RASs have been shown to be connected to PIs virological failure frequently. Mechanistically, the presence of RASs reduces the cure rate of PIs because conformational changes in the viral protease make it more challenging for PIs to bind tightly to the therapeutic target, which lowers SVR [3]. Stabilizing the interaction requires building a salt-bridge network structure between Q80, R155, and D168. On the other hand, the R155K mutation

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prevents the formation of the salt bridge structure, which lowers the stability of the drug-protease interaction. Clinical investigations have also revealed that the RASs of NS5B inhibitors are present during therapy, and based on the preceding rationale, HCV polymerase inhibitors can be classed as NIs and NNIs. In vitro investigation of the S282T variation revealed that the mutant polymerase creates mutations with lower affinity for the NIs after NI therapy, resulting in a considerable loss of therapeutic effectiveness. NNIs have lower resistance barriers than NIs because they attach to allosteric binding sites, which is far away from the polymerase active site [3].

4.2. The potential for drug resistance after DAA treatment

Beyond drug resistance, the safety of generic versions of DAA in clinical use is also a significant issue warranting continuous attention. Over recent years, HCV patients have steadily risen, particularly in LMICs. In contrast, the WHO recognizes DAA as the most effective treatment for HCV due to its remarkable success in achieving SVR. However, the current scenario sees DAA production concentrated in developed nations, accompanied by high prices restricting its accessibility for most patients in developing countries. This discrepancy has given rise to generic versions of DAA, which have emerged as more affordable alternatives to the original medication in the global market. This affordability is crucial for enabling more patients to access treatment. However, having addressed the price issue, the safety of it was focused. Although some studies have shown that generic DAA has shown as low side effects as original DAA in the treatment of HCV, the relevant data about the safety of generic DAA was reported in studies from small number of countries [15].

Consequently, the landscape of clinical research about the safety of generic DAAs is constrained, characterized by small sample sizes, limited data, and short-term observations. This restricts the extent to which valid conclusions can be drawn regarding the safety of generic DAAs. In essence, the safety of DAA generics remains an unresolved concern. Moving forward, a comprehensive approach demands more extensive and long-term clinical studies, substantial follow-up, and accurate research data to validate generic DAA medications' safety effectively.

4.3. The potential for drug resistance after DAA treatment

Lastly, when HCV patients undergo DAA treatment while concurrently using other medications, potential interactions can arise wherein some drugs have similar or opposing effects. These interactions might bring about changes in the absorption or metabolism of DAA, consequently impacting its effectiveness or contributing to adverse reactions. Experimental findings have indicated that the body's pH level can influence absorption. For instance, co-administering acid-suppressive medications and velpatasvir (an NS5A inhibitor, one of the DAA classes) for a brief period could result in a nearly 50% reduction in the efficacy of the DAA. Another study revealed that combining sofosbuvir (an NS5B polymerase inhibitor, another DAA class) with certain antiarrhythmic drugs like amiodarone could trigger severe bradycardia, which poses long-term risks. With the wide application of DAA across diverse HCV patient populations, the probability of DAA use has increased among elderly patients, individuals with pre-existing medical conditions, and those concurrently taking multiple medications. This scenario can lead to potentially diminished DAA effectiveness and heightened occurrences of side effects, particularly if the patient group is utilizing DAA in conjunction with drugs that should not be taken concurrently [16].

5. Conclusion

DAA therapy has emerged as the preferred and transformative clinical approach for managing HCV, resulting in a remarkable upswing in cure rates for individuals with HCV infection. The widespread adoption of DAA therapy not only facilitates the achievement of SVR reaching up to 90% among HCV patients but also offers broader benefits by repairing immune damage and effectively regulating blood glucose levels in the affected population. However, the utilization of DAA therapy on such a vast scale brings to light certain limitations, including the potential for drug resistance, concerns regarding the safety of DAA generics, and the intricate interplay of DAA efficacy when used

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concomitantly with other medications. Therefore, it is essential to decrease the rate of resistance mutations through researching antiviral drugs suitable to improve SVR further, to improve the safety of DAA generics through multifaceted, large-sample clinical studies, and to develop linkages between DAA and other medications through further research to improve medication use and increase the curative effect of DAA. These areas remain the focus of future research, and based on the extensive knowledge base of in-depth studies, it is hoped that more effective treatments will emerge.

References

[1] World Health Organization. Hepatitis C. July 18, 2023. Retrieved on August 24, 2023. Retrieved from: https://www.who.int/news-room/fact-sheets/detail/hepatitis-c

[2] Petruzziello, Arnolfo et al. "Global epidemiology of hepatitis C virus infection: An up-date of the distribution and circulation of hepatitis C virus genotypes." World journal of gastroenterology vol. 22,34 (2016): 7824-40.

[3] Zeng, Haiyan et al. "Direct-acting Antiviral in the Treatment of Chronic Hepatitis C: Bonuses and Challenges." International journal of medical sciences vol. 17,7 892-902. 15 Mar. 2020,

[4] Manns, M P et al. "Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial." Lancet (London, England) vol. 358,9286 (2001): 958-65.

[5] Kwong, A D et al. "Hepatitis C virus NS3/4A protease." Antiviral research vol. 41,1 (1999): 67-84.

[6] Manns, Michael P., et al. "Potency, safety, and pharmacokinetics of the NS3/4A protease inhibitor BI201335 in patients with chronic HCV genotype-1 infection." Journal of Hepatology, vol. 54, no. 6, 2011, pp. 1114–1122

[7] Kamal, Sanaa M. "Hepatitis C treatment in the era of direct-acting antiviral agents." Hepatitis C in Developing Countries, 2018, pp. 209-246

[8] Brody, Tom. "Mechanisms of action—part IV (infections)." Clinical Trials, 2016, pp. 635–662

[9] Pawlotsky, Jean-Michel. "NS5A inhibitors in the treatment of hepatitis C." Journal of hepatology vol. 59,2 (2013): 375-82.

[10] Gitto, Stefano et al. "NS5A inhibitors for the treatment of hepatitis C infection." Journal of viral hepatitis vol. 24,3 (2017): 180-186.

[11] Llorens-Revull, Meritxell et al. "Partial restoration of immune response in Hepatitis C patients after viral clearance by direct-acting antiviral therapy." PloS one vol. 16,7 e0254243. 9 Jul. 2021

[12] Shrivastava, S et al. "Augmentation of hepatitis C virus-specific immunity and sustained virologic response." Journal of viral hepatitisvol. 24,9 (2017): 742-749.

[13] Drazilova, Sylvia, et al. "Glucose Metabolism Changes in Patients with Chronic Hepatitis C Treated with Direct Acting Antivirals." Canadian Journal of Gastroenterology & Hepatology, U.S. National Library of Medicine, 3 Oct. 2018,

[14] Dawood, Alaaeldin Abdelsalam, et al. "Factors associated with improved glycemic control by direct-acting antiviral agent treatment in Egyptian type 2 diabetes mellitus patients with chronic hepatitis C genotype 4." Diabetes & Metabolism Journal, vol. 41, no. 4, 2017, p. 316,

[15] El-Nahaas, Saeed M et al. "High sustained virologic response rate using generic directly acting antivirals in the treatment of chronic hepatitis C virus Egyptian patients: single-center experience." European journal of gastroenterology & hepatology vol. 30,10 (2018): 1194-1199.

[16] ZHANG X, LI Yunguo. Current status and problems in the application of direct antiviral drugs for chronic hepatitis C[J]. Journal of Clinical Hepatobiliary Diseases,2018,34(4):853-857.