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Review Article

Combating Hepatitis C (HCV): A Review of Present and Future Perspectives

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Abstract

Over the past few decades, the race against the treatment strategies of infectious HCV has gained a lot of momentum. These treatments include several therapies like Ribavirin, INF-α, DAA based pro-drugs, vaccines, and even naturally occurring compounds like herbal extracts as well as scorpion venom. All of these drugs have their specialized techniques and methodologies of administration such as combinatorial therapies of several of these drugs combined that are proving highly useful and constantly evolving along with the technological evolution. The main problems that are associated with combating Hepatitis C include the phenomenon of drug resistance and highly diverse genotypes of HCV. In this review, we have tried to discuss the overall research on these treatment methods and their basic ups and downsides of each briefly.

Keywords: Hepatitis C, HCV, Ribavirin therapy, Interferon therapy, HCV vaccines

Introduction

Hepatitis C virus belongs to the class of viruses known as hepacivirus of family *Flaviviridae.* Several treatment strategies are available and have been applied successfully to combat the virus that causes the deadly hepatitis C in humans. These modern drugs and methods have been proven useful in more than 90% of the cases (46). The common therapy that has been utilized for a long time is the combination therapy of Ribavirin and INF-α that was used all over the world until the arrival of more potent and modern medicines like DAA's etc. The chronic condition of the Hepatitis C virus affects 2-3% population of the world as reported. It is highly contagious and is transmitted to others via blood and other body fluids. It progresses from acute to a chronic stage spontaneously and its symptoms include fatigue, bleeding, jaundice, mild fever, and other muscle-related weaknesses.

The most common and important complications caused by HCV in its patients include liver cirrhosis, fibrosis, and Hepatocellular Carcinoma. Other complications related to the infection are highly random and diverse over a large number of patients based on the type of genotype the patients are infected with. It has also been reported that Diabetes Mellitus that is caused by a buildup of Multifactorial Insulin Resistance is linked to increased risk of Hepatocellular Carcinoma, a higher level of transplant rejection in liver patients, increased risk of fibrosis and other related complications. Over the past few years, scientists have tried to combat HCV using very potent methods and diverse kinds of approaches that have led us to these modern and advance ways of treatment and cure. The most effective and modern procedures used nowadays include Ribavirin, INF-α, Direct Acting Antivirals (DAA's), RNA techniques, Vaccines, and other potent

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agents. These can be used in combination like some triple therapy procedures based on the severity in patients of different genotypes.

Ribavirin

In the race of producing a broad spectrum drug against several RNA and DNA viruses like HCV and HIV, Ribavirin is one of them. Ribavirin is a guanosine nucleoside analog that attacks the mRNA synthesis process of HCV to inhibit its replication. Ribavirin is a very potent agent with a single dose elimination half-life of 43.6 hours and a multiple-dose elimination half-life of 298 hours (78). Because of its fewer side effects relative to other drugs and its lower half-life, it is considered as the top treatment choice in HCV therapy. Ribavirin acts on the virus by a novel hemolytic mechanism in which *in vivo* hemolysis of the HCV takes place. HCV is immune to several other commonly used agents but ribavirin has shown a promising increase in SVR rates during the course treatment. HCV causes a state of the liver called a pro-inflammation state (60). When HCV progresses to its chronic stage, it became very difficult to treat. By using Ribavirin therapy, patients with chronic Hepatitis C conditions have shown improv-ement in sustaining a good virological response. One major side effect during Ribavirin therapy is hemolytic anemia caused by the aggressive action of Ribavirin in Hepatitis C patients. Studies have been made on drug delivery of ribavirin analogs that is highly specific to only liver cells but the process is still in phases of developments and trials have begun in several areas around the world (70). Experiments have shown that Ribavirin-L-Val-GCDCA is a highly targeted offside analog of Ribavirin that acts directly on HCV with no other complications to other healthy cells (11).

Although the hemoglobin levels have been declined with an increasing persistent dose of Ribavirin yet some patients with SVR achieved have shown sustained lower normal limit hemoglobin levels (24). It means that predicting the anemic condition of patients based on Ribavirin therapy is an inefficient method with unstable probability (67). It has also been observed that the less the levels of hemoglobin the more effective the treatment is and the patients with high SVR rates and who are responding well to Ribavirin therapy automatically have lower hemoglobin levels and vice versa. So, we can infer how good the treatment is going based on the patient's hemoglobin levels with some other crucial factors (76). The mode of action of Ribavirin against HCV is currently unknown due to its synergistic effects concerning other potent agents (Combination therapy) (23). Ultra-deep sequencing revealed that Ribavirin acts on HCV by lethal mutagenesis strategy that is also utilized by the other drugs of the same category (2). In lethal mutagenesis, there is an intermediate state of transitions that takes place that is mostly G-to-A and C-to-U transitions (7). These transitions disrupt the genome of HCV in a way that its replication ability gets lost that forward with the elimination of the virus (4).

Double dosing is usually not recom-mended in Ribavirin therapy, but in a randomized trial evaluation study, by doubling the dose patients achieved SVR rates very early as compared to the normal dose, and ultimately the span of treatment reduced greatly (3). In addition to the normal Ribavirin therapy, the mode of action of Ribavirin also influenced the production of interferon from plasmacytoid dendritic cells (pDC) that is a potent agent against HCV.

Ribavirin influences receptor 7 and 9 on these cells (18). This stimulation causes enhanced production of INF-α from these cells. To deal with the anemic conditions during this HCV therapy, L-Carnitine supplementation has shown promi-sing results by efficiently maintaining the level of production of hemoglobin in the body of patients (31). A little higher level of SVR rates has also been observed by a sustained amount of hemoglobin in the blood. Ribavirin mode of action against several RNA and DNA viruses is mostly based on the genotype it is interac-ting with. Crimean Congo Hemhorrgic Virus (CCHF) is a type of virus that uses ticks as a vector for its transmission. Ribavirin therapy has shown great potential for the treatment of CCHF in

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several cases (15). Even though Ribavirin shows great potential against HCV yet nature plays in its way. Many Ribavirin resistant mutants have been reported in recent years of research. This resistance against Ribavirin is mostly because of the accumulation of mutations in patients through-out therapy that ultimately contribute to the rise of these mutant strains (25). To combat this problem, mostly combination therapies with other anti-HCV potent agents with Ribavirin are utilized based on the conditions posed by these strains (6).

Other Potent Nucleoside Analogues

Ribavirin no doubt is highly potent in its action but it is not the only one to have such potential against HCV. There are other effective nucleosides analogs present like Tri-cyclic 2′-C-Modified Nucleosides, β-D-2′-deoxy-2′dibromo nucleosides, C Nucleoside GS-6620 and Nucleoside Polymerase Inhibitor RO5855, etc. Tri-cyclic 2′-C Modified Nucleosides have anti-HCV activity due to a mechanism of substitution called di-substitution at the 2′ position of the nucleoside molecule. This type of nucleosides attacks on HCV by disrupting the functioning of right-hand RNA polymerase required by HCV for replication. (62) β-D-2′-deoxy-2′dibromine nucleoside types are very selective in their anti-HCV action. The pro-drug 13a derived from this analog has shown the most potent activity against HCV in both *in vivo* and *in vitro* trials (63). Similarly, C Nucleoside GS-6620 Mono-phosphate Pro-drug is also highly selective in its action. It uses a novel mode of action called Pan-Genotype activity that has major advantages over other treatment methods like highly reduced drug-drug interactions phenomenon and a steep barrier for HCV to be able to produce resistance against it (74). Nucleoside Polymerase Inhibitor (RO5855) is also another cytidine inhibitor. RO5855 is mostly used in combination with Ribavirin as a combination therapy for the best results. It also doesn't show any kind of unfavorable interaction with Ribavirin in general that makes it a suitable candidate for use on different genotypes.

Simple Interferon Therapy

Interferon has shown great potential against HCV as shown in different studies that include it as a main agent but interferon is mostly used as an effective agent in combination with Ribavirin and other closely related drugs. Patients treated with only Interferon show a stable and sustained SVR rate in most of the trails and other studies. Furthermore, the response to interferon therapy is also diverse over patients of different genotypes. For example, patients with genotype HCV-1b show a very poor response to INF therapy while patients with genotype HCV-2a exhibit the most response. The effectiveness of the treatment including interferon can be increased exponentially when used in combination because interferon acts as a catalyst as can be seen in combination therapies that include Ribavirin-Interferon pair (14, 51).

Interferon + Ribavirin (Combination Therapy)

Ribavirin and Interferon, both are potent agents and first-choice treatment option in HCV therapy. In modern researches, scientists developed new techniques of treatment for HCV. It has been seen that when Ribavirin and Interferon are used in combination clinically, they both show some kind of synergistic association with each other (66). This association makes this combination therapy the first and foremost choice while dealing with HCV. (8) The synergistic mechanism of both of them is very complex in their mode of action. Recent indications show that Ribavirin enhances the expression of Interferon specific genes (ISG). Ribavirin influences the STAT and JAK signaling pathway for interferon (19).

STAT 1 and STAT 3 phosphorylation mechanisms were also boosted as seen during *in vitro* experimentation. The internal ribosome entry site (IRES) mediated translation was observed by a team of scientists in specific Huh–7 cells (28). The synergistic relation of both Ribavirin and the Interferon were then verified later by CalcuSyn and MacSynergy deep analysis softwares (66). It was seen in a study that a proper

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response was achieved was produced against HCV in 16 out of 21 patients that were under this conjugate therapy. It was a 96-week treatment span with efficacy of more than 75%. This study also suggests that conjugate therapy is more effective as compared to Interferon only over a treatment span of 24 weeks (79).

Triple Therapeutic Procedures

Recent advances in Ribavirin and PEGylated INF-α therapy have produced a new way of treatment. This is termed as a triple therapy procedure. As it is understood from the name, it utilizes an extra potent agent with previous combination therapy of Ribavirin and interferon combined provided that the agent must have a stable complex formation. *Nitazoxanide* is a type of agent that has a potency to enhance the action of combination therapy through several mechanisms (27).

Patients treated with this triple therapy have shown relatively even SVR rates than that of combination therapy alone (57). *CIGB-230* is another synthetic agent that is utilized with combination therapy for producing a lympho-proliferative response against antigens. It superimposes the IgG immune response to the HCV. Patients treated with this triple therapy showed a higher SVR achievement rate that is mostly stable for longer periods (16).

Mericitabine utilization shows the reduced impact of specific IL28B genotypes on RVR and cEVR rates as compared to other agents. There is also no reported case of any pharmacokinetic drug-drug interaction of *Mericitabine* with Ribavirin (5, 30).

During all these therapeutic procedures, the levels of HCV core antigen (HCVcAg) have great importance in predicting the extent of the succession of therapy. The prediction of re-emergence of RNA in ongoing conjugate therapy of Ribavirin and peg-INF is done by measuring the HCVcAg levels in patients and then a statistical model is constructed to infer the final results (12). The relative levels of Natural Killer Cytolytic activity are always considered in an ongoing conjugate therapy of Ribavirin and Interferon (17). The HCV infected targets are influenced by NK Cytolytic activity levels but the deep sequencing and modeling analysis revealed that this specific activity is the main cause of liver damage associated with HCV induced complications (60). In reality, regardless of all these applied therapeutic procedures, the HCV residual persistence has been a major issue in the past couple of years (22). It has been reported that HCV could rose from the dead due to the remains or residuals that go on circulating in the body and again may cause infection when conditions become favorable (26). These results were obtained after liver biopsies and examining the lymphoid cells after the treatment cycles of patients were over. These dormant stages of HCV in the body have main contributions to the re-emergence of infections in the body. That's the reason behind the suppression effect that goes on decreasing with time during treatment. However, the efficacy of triple therapy is significantly higher than normal conjugate therapy (21).

Direct Acting Antivirals (DAA's)

Advances in the era of medicine keep on going in analogy with Darwinian evolution itself. Direct Acting Antivirals are a new breed of treatment options for viral diseases like HCV, HIV, etc., not to mention it is one of the most modern and effective approaches to deal with viral diseases nowadays. DAA's are used in case every other treatment option fails to induce a proper SVR rate in HCV infected patients. The use of these antivirals has revolutionized the way we combat viral diseases. One of the major perks of using these antivirals includes the brilliant efficacy percentages in clinical trials sometimes even more than 90%. These antivirals came into existence by examining high throughput replicon models. Due to the introduction of DAA's, the sustained SVR rates of more than 95% have also been seen in some patients (10).

DAA's show some promising future treatment strategies for HCV and other infectious diseases. Furthermore, in the application of DAA's, the predictable drug-drug interactions have proven to be highly favorable. For

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example, Ritonavir is used against HIV as a DAA but it has no potent effect on HCV. But the pharmacokinetic study revealed that it can be used as a CYP3A inhibitor. That's the reason for using *Ritonavir* with other combinations of antivirals improves half-life. This is also termed as *Ritonavir* boosting procedure. The NS3/4A Protease Inhibitors like *Telaprevir, Simeprevir,* and *Boceprevir* has been approved for use with the conjugate therapy of Ribavirin and Interferon (39). They have shown great potential in achieving high SVR rates in no time as compared to conjugate therapy only but the associated side-effects like anemia and inhibition of an important drug-metabolizing enzyme Cytochrome P4503A4 (CYP3A4) are still one of their major concerns (1). *Pibrentasvir, Ombitasvir, Elbasvir,* and *Ledipasvir* are highly potent NS5A inhibitors for HCV genotype variants from 1 to 6 containing the NS5A site. The 50% effective concentration causes *Pibrentasvir* to stabilize the overall suppression with ranges of 1.6 to 5.0. It means that it has a great potent activity over a large number of variants of HCV. It has also shown a great improvement in SVR rates when utilized with conjugate dual therapy (58). Similarly, *Samatasvir* is another NS5A inhibitor. It has an additive role in conjugate therapy. It is used as a pro-drug IDX184. The advantage of using *Samatasvir* over other DAA's is its consistency of action over a large number of genotypic variants that make it a crucial addition in most therapies (37). For the proper action of most NS5A inhibitors, the NS5A site is the most attractive one and has crucial importance in the formation of stable complexes. The NS5A polymerase inhibitors work efficiently on this site as seen in Multiplee-Pharmacophore modeling procedures and Random Forest Simultaneous Combination Analysis (69).

Mericitabine (RO5855) is also a Nucleoside Polymerase Inhibitor. It is also used as an additive with simple Ribavirin therapy. By using Prichard's model-based synergy analysis, it has been proved that RO5855 is one of the best additive choices with Ribavirin in HCV treatment. There is also a genotypic association of using DAA's with anemia as seen in modern data obtained. For example, *Faldaprevir, Declatasvir,* and *Deleobuvir* are also types of DAA's. These both induce anemia in patients of different genotypes but it is also observed that there is no decline in SVR12 rates when interferon-free *Faldaprevir* and *Deleobuvir* were used in combination with Ribavirin. This shows the promising use of both of these in related genotypes that support proper and sustained SVR rates (67).

Sofosbuvir (NS5B inhibitor) and *Declatasvir* used in combination have also shown very good SVR rates in patients with HCV-Genotype 1 infection over 12 weeks of continuous data analysis. The lower adverse effect profiles of several patients confirm the effectiveness of this combination (83). The response rates of treatment are also improved in continuous therapeutic procedures (13).

Signal Peptide Peptidase (SPP) is an aspartic protease that is mainly involved in the maturation of the core protein of HCV. Some types of DAA's inhibitors disrupt this maturation process and ultimately inhibit the proliferation process of HCV (65).

α-ketoglutarate-dependent dioxygenase is an obesity-associated protein also known as *FTO.* It is involved in the management of body weight and regulation of energy throughout the body. Type 2 Diabetes Mellitus is associated with this FTO related instability of *rs9939609 polymorphism.* In recent experimental studies, it has been reported that this polymorphism is associated with the acute resistance to several DAA's due to its complications in patients like type 2 Diabetes Mellitus, Insulin Resistance, and obesity (9). No doubt, the treatment with Direct Acting Antivirals (DAA's) in combination with standard Interferon-based therapy has produced positive and exceptional results against HCV but factors like these have to be considered before deploying a lethal treatment option with possible complications (58). Multi-scale Mathematical models of DAA's action (intra and inter-cellular dynamics) against HCV infection have shown very promising results with over 90% effectiveness. Other mechanisms of action against HCV have also been observed after the analysis of complex models (38). *Very-low-density Lipoproteins*

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(VLDL) are mostly associated with aiding the HCV in its replication and helping in gaining entry to the cell. A very low level of SVR in patients with high levels of VLDL is common. This seems to be a type of indirect relationship between levels of VLDL and the effectiveness of drugs that have been applied during treatment. On the other hand, patients with very low levels of VLDL have shown good response rates to the therapy as well as better SVR rates as compared to patients with high levels of VLDL (40). Furthermore, the overall efficacy was higher than expected in both RVR and SVR analysis conditions. The overall pooled SVR and RVR were 95% and 97% when second-generation DAA's were used. All of these percentages were constant over the patients infected with HCV-3, HCV-1, and HCV-6 (80).

RNA Based Therapy

Ribavirin, Peg-INF, and DAA based therapies only have taken another step in the race of treatments related to HCV but all of these therapies have their drawbacks like being expensive and may contribute to the progression of severe hemolytic anemia, etc.

Recently developed gene silencing techniques that involve the use of specifically designed siRNA or miRNA strands and viral vector-based gene delivery mechanisms are being used in most modern treatment strategies (50). For example, ITPase is the main enzyme that is involved in the replication of HCV. ITPase inhibition in HCV transfected Huh-7.5 cells by utilization of siRNAs have shown that the HCV proliferation in patients can be controlled progressively and effectively (72). Only a few numbers of patients with different ITPA genotypes have shown some signs of anemia but no severe conditions were inferred. This happened because of ITPA polymorphism (20). In preclinical evaluation studies, miRNA sequences gained entry to the cells and replaced the RNA of HCV with exact copies that are a complementing mirror to the genome (61). This procedure has proven successful because it effectively inhibited the replication process of HCV in up-to 95% of cases within 2 days span. It was impossible to achieve with simple Ribavirin and INF-α based therapies that only have comparably low effectiveness (64). These miRNA sequences have been developed using the studies of the internal ribosome entry site (IRES) that involves the cap-directed translation process of siRNA in mice (68). Designing these RNA sequences is a very difficult task because it involves the extensive use of Bioinformatics based modeling and analysis. *In Silico* Studies of two siRNA variants, HCV353 and HCV258 sequences have shown the potential of specific potent design of siRNA (71).

These two variants produced a very high antiviral activity because of their very short exposure time as well as low usage concentrations. Thus, they provide a way in the development of very efficient Oligo-nucleotide based drugs with very fewer complications relative to other treatment options. In a study, the efficacy percentages were higher than expected when siRNA 361 was targeted in the 5'UTR region. The higher level of suppression confirms the efficacy of the treatment. The number of mutant strains of resistance was also reduced (81).

But this siRNA requires some kind of effective drug delivery system. At this point, the nanotechnology will take hold of the ground. Delivery of siRNA by utilizing lipid-based Nano-particles is a very effective way of injecting sequences into the genome of HCV (29). It has comparably high effectiveness because these approaches use non-classical ways of transference that ultimately induce a very diverse range of immune responses as shown in several experimental studies. The more specific and targeted *in vivo* delivery systems include the use of α-tocopherol (Vitamin E) based on Nano-particles. The effectiveness and safety of α-tocopherol coupled Nano-particles make them an effective way of drug delivery even with other combinatorial HCV therapies (72). In some approaches, the siRNA has some kind of off-target inhibitory effects. For example, the MOBKL1B siRNA sequence shows some off-target effects but they are still not a major

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concern compared to complications induced by other therapeutic methods (77).

Vaccines

There are also some experimental vaccine options for treatment available that can play an important role in the therapy of HCV when used in combination with other agents. For example, the MF59 adjuvant based HCV E1 E2 vaccine has induced various immune responses by *in vivo* induction of various lymphoproliferative pathways over the controlled course of treatment. Three dosage levels were used in patients that were tolerated by most of the candidates present in the study (53). There is also another study of vaccine-related experimental treatment applied to chimpanzees that were infected with both HIV-1 and HCV at the same time. Vaccines for either of the viruses in serology show better than expected responses when administrated in this specific condition of infection. This means that patients with both of these infections can be treated for both infections simultaneously when using an experimental vaccine based therapeutic method of treatment (59). There is one major problem that HCV cleaves of the activated Rig-I pathway to enhance its ability of replication. In these conditions, a vaccine cannot work efficiently because even the innate immune responses are suppressed completely. By using NS5A polymerase inhibitors the innate immune responses can be realigned by restoring the activated Rig-I pathway that ultimately superimposes the action of administrated HCV vaccine (75).

HCV masks its expression while continue to replicating unchecked in the body if not treated on time. This happens because of very less threshold level of antigen signaling required for an effective immune response is produced due to this masking camouflage strategy utilized by the virus. The mechanism can be understood if we can understand the interaction of viral envelope glycoproteins with administrated vaccines that in the present day scenario is a little bit difficult because of the diverse distribution of genotypes of HCV. However, some immunity-enhancing prophylactic procedures have been developed by understanding the mechanisms of these surface glycoproteins (52). Furthermore, the efficacy of treatment options that include vaccine is still very low and requires highly organized clinical trials that have just begun (82).

A recent study was conducted on injecting naked DNA of HCV into the patients to observe its immunogenic effects on the natural immune system but a very low level of immune response is produced. However, when NS5A and rNS5A residues associated with RNA were used along with DNA, there was an immediate increase in the production of both CD4+ and CD8+ T-Cells, a release of a large number of cytokines, and also the production of a large number of anti-NS5A antibodies (47). This means that when the combined effects of both the DNA and using RNA based NS5A and rNS5A in conjunction is significantly higher than that of using the viral DNA only (51). DREP vaccines were studied in mice transfected with an enhanced strain of HCV known as Ankara HCV. This modifies strain represent the full-length genome of HCV and is highly useful in the study of newly developed therapeutics like vaccines. When mice are injected with DNA launched RNA replicons, the DREP vaccine displayed a potent action by significantly increasing the CD4+ and CD8+ T-cell counts against Ankara HCV (35). However, there was a huge subversion of T-Cell responses when high dosages of those vaccines were used that are virally vectored (73). Some adenoviral, as well as vaccines against Ankara, have also shown the subversion phenomenon (59). These drawbacks can be overcome if a high and sustained amount of immunological memory can be produced in the subject. Furthermore, this may require a great deal of research on other vaccine delivery vectors (54).

Treatment Alternatives (In Development)

Studies related to treatment strategies of HCV have a very wide range of span and include those novel mechanisms that may be the key to

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the cure of HCV that are currently under extensive research. It is reported that HCV utilizes both extrinsic and intrinsic pathways to mediate apoptotic activity that is the main cause of liver cirrhosis and fibrosis. The up-regulated markers along with these complications include caspases, tumor necrosis factor, etc (45).

In recent years of research, many natural compounds have been identified for their potent anti-HCV action. For example, *Glycyrrhizin* is a compound that is extracted from the roots of the licorice has shown potential in the prevention of hepatocellular carcinoma in patients with long and severe chronic infection. It acts through some kind of novel mechanism that is yet totally unknown. Another effective entry inhibitor is *Ladanein*. It has more effect on viral assembly than its replication. Certain plant extracts also possess some level of antiviral activity because these plants have one of the following active chemicals like *flavonoids*, *saponins*, and *lignins*, etc. These types of chemicals have the potential to inhibit the HCV protease as recent research on these compounds suggests. Herbal extracts of herbs like *Tranchyspermum Ammi* also inhibit HCV protease activity while methanol like an extract from *Swietenia macrophilia* inhibits HCV replication *in vitro* for Huh-7 cells (33).

Venoms from different animals like scorpion and snake have also been an important part of the race of treatment against HCV. These venoms have biologically active antimicrobial peptides that have a highly potent virucidal activity. That's why these are extensively researched for the design and in the modeling of drugs against HCV (32). Anacardic acid is a phytochemical that has shown effects on different stages of the HCV life cycle. It is because it affects various enzymes like *Histone Acetyl Transferase* that are needed for replication by the virus (44). Furthermore, there also no possible recorded effect of Anacardic acid on cell viability and stability. It also cuts off vascular endothelial growth factor signaling of HCV (41).

There are very-low-density lipoproteins that are naturally present in the human body. These VLDLs have some kind of inhibition effect on HCV as studied in a humanized mouse model. Studies also suggest that the lower the concentration of these VLDLs the higher the infectious activity of HCV. These VLDLs now serve as a base for drug designing of most modern HCV therapeutics (40). Some other synthetic drugs are based on modeling of these natural compounds like *Hydroxyzine pamoate* and *Benztropine mesylate* that are used in combination with other agents for their property of selective inhibition (34). These drugs are clinically approved and form the basis for the targeting potential in other drug models (43). There is also a novel inhibition mechanism mediated by heat shock proteins like HSPB8 (Heat Shock Protein-B8) and DNAJC5B. By applying some effective and modern gene silencing techniques on these proteins, a burst of replication in HCV was observed. It means that there is a mechanism of inhibition that is not yet understood mediated by heat shock proteins of a cell (48). Similarly, in another research, Pyruvate Dehydrogenase Kinase (PDK) provides HCV with nucleotide precursor molecules that mediate its replication process. Somehow by blocking PDK activity, the replication process can be properly controlled (42).

Multi-Drug Resistance Phenomenon

A phenomenon exists in various HCV genotypes called the multi-drug resistance that helps HCV to escape all treatment strategies through a series of specific mutations in the genome. (56) For example, the HCV genotype 3a is a Cytosine-Thymine (CT) and Thymine-Thymine (TT) variant. It does not respond to all possible combinatorial procedures of modern drugs (49). This phenomenon of multi-drug resistance can be understood by extensively analyzing the mutations in *E2-PePHD* regions of HCV that make it resistant to the therapy of INF-α as well as other drugs. This otherworldly resistance phenomenon of genotype 3a is not yet understood completely.

The genotypic turnover of HCV is more common in patients under hemodialysis treatment because the resistance can develop due to blood-borne spread to the niche (55).

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But this can be avoided by applying better sanitary measures and preventing any blood-borne viral contact (36). Over the years, this phenomenon of resistance is constantly increasing and cause trouble to the researchers.
Analytic techniques developed using computational modeling have their time-related perks but these models can't produce the exact real-world conditions because of a massive number of factors that are interacting with each other in a specific condition.

Discussion

In the present, although we have developed extensive and more advanced treatment methodologies still we are facing heavy casualties in combat with HCV. In this article, we have discussed the use of different techniques of administration of Ribavirin and other related analogs in patients with HCV.
Ribavirin has produced very good results in the inhibition of HCV replication as well as achieving better SVR rates relative to previous treatment drugs. But it has major side effects like hemolytic anemia etc. Even with the combination therapy that includes INF-α, the risk of anemia has not reduced at all. Furthermore, this combination type technique has only been seen as successful in less than 50% of the patients. Due to these drawbacks of Ribavirin and INF-α, therapeutics like DAA based pro-drugs and techniques like using siRNA are only a little more efficient as compared. DAA base pro-drugs paved the way to a more successful treatment but these are very expensive to be used as normal treatment medicines. Similarly, the siRNA method is also very expensive and has its downsides like off-target action, etc. Vaccines are also under development due to the phenomenon of severe multidrug resistance and diverse genotypes of HCV. Meanwhile, treatment through natural compounds like Herbal Extracts of Medicinal plants and Scorpion Venom is under study. Nowadays, researchers are only using it for drug designing and modeling. Studies and research on novel methods of treatment against HCV are on peak and improvement of previously existing methods is in motion.

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