Hepatitis C therapies: A chronology of Past, Present and Future Strategies

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The key role of antiviral therapy of patients with chronic HCV is the sustained eradication of HCV. Different therapeutic plans such as herbal formulations against hepatitis symptoms were put forward for hundreds of years. However, lesser efficacy and adverse effects constrained the large scale use of herbal medicines. The modern approach, thrived after the discovery of HCV made use of “interferon-based” regimens in different dose, duration of treatment and combination. After, ribavirin used in combination with interferon alpha became the centerpiece, pegylation of interferon alpha also aided in enhancing the efficacy of therapeutic plans. Keeping in view the genotype of HCV, viral load and virologic response to treatment, pegylated interferon alpha in combination with ribavirin soon became the standard of care for treating hepatitis C. Adverse effects and lower sustained virologic response rates associated with “interferon-based” regimen made indispensable the search for novel HCV therapies. The direct interference of some drugs in the HCV life cycle opened new gates to the treatment strategies beyond interferon. HCV NS3/4A protease inhibitors, the first developed class of Direct Acting Antivirals provided the modern world with Telaprevir and Boceprevir like drugs, that increased the SVR rates up to twice or thrice as that of Standard of Care alone. Many other important direct acting antivirals including polymerase inhibitors, alphaglucosidase and cyclophilin inhibitors, Nitazoxanide and immunomodulatory therapies proved effective in increasing the upshot rates of HCV therapies. Recent advancement saw the upstart of direct acting antiviral combination therapies and more direct acting drugs under different phases of clinical trials.

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Hepatitis C has been reported as a serious common transmissible disease, having hepatic and non-hepatic manifestations such as hemorrhage in the digestive tract, fibrosis, cirrhosis, and liver cancer[8]. Having a different prevalence ratio in different regions of the world, HCV is a globally incident pathogen impacting about 130-170 million people worldwide[2,3]. 70% of all the infected individuals develop chronic HCV infection and 20% adopt liver cirrhosis which may ultimately lead to hepatic carcinoma[4]. The standard ‘interferon-based’ regimens had evolved as the backbone of standard of care (SOC) against HCV[5]. “Interferon-based” regimens evolved from IFN monotherapy to the combination of ribavirin and ultimately the pegylation of interferon. The treatment outcome i.e. SVR associated with IFN monotherapy to the combination of ribavirin and ultimately the pegylation of interferon. The treatment outcome i.e. SVR associated with IFN based therapy increased with its evolution thus pegylated interferon having greater SVR rates associated with it[6]. However, “interferon-based” therapy has several limitations in terms of adverse effects and lower response rates in the majority of patients[7]. Therefore, the focus shifted towards the development of therapies ahead of interferon resulting in the discovery of a wide array of anti-HCV drugs that stops further generation of the virion by blocking various indispensable steps of viral replication and assembly[8]. This review focuses on the present, future assessments in the field of antiviral treatment and finally on intensive efforts for the designing and optimizing new anti-HCV drugs.

HISTORICAL PERSPECTIVES: TRADITIONAL APPROACH TOWARDS HEPATITIS C TREATMENT

Traveling from the folk ways of treatment towards the advanced therapeutic strategies, it might be anticipated that the long-term
approaches must have been in practice for thousands of years for hepatic disorders[10]. Ayurveda, that is in existence for about 5 000 years was used to treat different types of maladies. It is a natural technique of treatment which works on the principle of prevention followed by cure practices. It involves spiritual and mental healing for promotion of good health and treats a disease by natural medicines. It recommends a specific way to normalize the liver which includes lifestyle changes, dietary advice, yoga and use of medicinal herbs. Ayurvedic medicines proved to be great hepatoprotective agents[39]. Many other herbs were used by the system to treat the liver ailments caused by hepatitis C or other viral infections. Some herbs with products obtained are Silybum marianum (Milk Thistle), Berberis aristata/vulgaris (Berberine), Andrographis paniculata (Kalmegh), Angelica archangellica, and Boerhavia diffusa etc.[11]. Silybum marianum is however controversial according to recent studies as some experiments have proved its inefficacy against HCV[39].

With the passage of time, focus shifted towards the Chinese herbal medicines which are in practice for the past 1000 years approximately[14,15]. Traditional Chinese Medicines (TCM), the Chinese herbs proved very effective and are still in practice with efficiency greater than the modern western medicines. In the international symposium held in April 1991, in Beijing, more than a hundred researchers approved the traditional Chinese medicines (TCM) to be most effective against the hepatic diseases including hepatitis C[15]. Ergil at the Fifth Symposium of the Society for Acupuncture Research Conference in 1998 stated that more than 55 herbal formulas are in use against hepatitis C according to a 1995 literature review[14]. Acupuncture is an important tool of Chinese medicines in which sterilized fine needles are inserted in the body at various points. Acupuncture therapy is a balancing tool which helps the human body to recover from various syndromes by regulating the blood flow[39]. A research paper by Cohen et al. (1998) presented at the 11th International Conference on AIDS, in Geneva Switzerland in 1998, referred to a study carried in 1995 on co-infection with HIV and hepatitis (B or C), inferring that acupuncture alone proved effective in regulating the production of hepatic enzymes[39].

The TCM also includes the use of herbs as drugs. Porter (2004) stated in an article that there are many types of herbs approved by the National Centre for Complementary and Alternative Medicines (NCCAM). Some are Kava, Blue-green Algae, Sassafras (Sassafras albidum), Dong Quai (Angelica polymorpha), Jin Bu Huan (Lycopodium serratrum), Comfrey (Symphytum officinale and S. uplandicum), Pennyroyal (Mentha pulegium), and Shark Cartilage etc. However, information regarding the use of herbs for hepatitis C is by no means complete. There are evidences about the disorders related to the simultaneous use of herbs with antiviral drugs e.g. the use of Bupleurum along with antivirals resulted in 16 deaths in Japan[36].

Similarly, toxic hepatitis is an adverse reaction resulting from the simultaneous use of herbal medicine with hepatotoxic ingredients such as acetaminophen and non-steroidal anti-inflammatory agents[27].

Natural medicines against HCV have been widely applied both solely and in combination with modern therapies i.e. Western medicines (discussed later). Medicines used in the therapies are classified into three categories called as Western medicines (“interferon-based” regimens), complementary and alternative medicines (Ayurvedic and Chinese medicines) and a combination of these two called the Integrative medicine[39]. Natural medicines only act mostly as hepatoprotective agents. Herbs act as healers of the damage caused by the notorious rival. They do so by regulating the activities of several enzymes in the liver. Andrographis paniculata, for example regulates glutathione reductase, superoxide dismutase, catalase, and, glutathione peroxidase. This and many others have been reported as a good antioxidant and promising hepatoprotective agents[18,19]. Similarly, many other herbal formulations such as silymarin have improved the disease state while acting as hepatoprotective agents. For instance, 650 mg/d of silymarin for 6 months in patients with chronic hepatitis C resulted in improved serum HCV-RNA titer, serum aminotransferases and patients’ quality of life. Silymarin has been demonstrated as anti-inflammatory and anti-oxidants, which aid in reducing hepatic inflammation and damage caused by HCV[17].

However, herbal medicines solely are less efficient in eliminating the virus from the body. So far, herbs are unsuccessful in viral load reduction and preventing relapse of the disease. Studies have shown that a very low proportion of subjects treated with herbal formulation alone reported an increase in serum HCV RNA. This calls for the need for further research and expertise in the area[39].

**PRESENT PERSPECTIVES: WESTERN APPROACH TOWARDS HEPATITIS C TREATMENT**

The discovery and Evolution of Interferon

Sir Alick Isaacs in 1957, started a new era when he found a human protein block the process of viral replication and was called as interferon[21]. Cantell’s group of Finland derived clean and fairly sufficient amount of IFN, which soon got a pivotal role in antiviral activities[22]. A therapy is said to be successful when the HCV becomes undetectable after 24 weeks of the treatment. The viral load should be 100 times less than the amount present before treatment. The viral load should be 100 times less than the amount present before treatment. This is known as the response to the virus to treatment[20].

After its approval by the FDA in 1991, more trials were made on the “interferon-based” therapies of hepatitis C. Its standard dose was set to be 3 MU (million units), three times a week for 3 months[23]. Interferon alpha-2b resulted in about 47% ALT normalization response and about 40% histological response in treated patients[21]. The studies of Poynard et al., (1996) favored 3 MU three times a week for 12 months for treating chronic hepatitis C, while it should be 3 MU three times a week for 3 months for acute hepatitis C[20].

The second type of interferon, which is known as Alpha-2a interferon (Roferon-A), approved by the FDA in 1996, bears only one amino acid difference from alpha-2b interferon and its standard dose was set as 3 MU three times in a week for 12 months. The overall efficacy of Roferon-A is the same as that of Interon-A[27,31]. Another type of interferon approved in 1997, called as consensus interferon showed a greater in vitro biological activity as compared to interferon 1[27,31]. However, Tong et al., (1997) suggested that consensus interferon is only slightly efficient as compared to the interferon 1[22].

“Interferon-based” therapy has many delimitations associated with it such as thrombocytopenia, neutropenia, neuropsychiatric disorders, headache, fever, chills, pain in joints, and myalgia[20,35]. Interferon is involved in amending the immunology of the recipients, resulting in autoimmune disorders such as thyroiditis, reported in 20% of patients subjected to IFN therapies[20,37].

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demonstrated to have sustained absorption, a slower rate of clearance and an extended serum half-life as compared to the peg-intron and intact interferon Alpha. The overall sustained virologic response rates were shown to be 36-39% with peg-IFN-alpha-2a monotherapy[49]. Pegysys was approved in October 2002 and the recommended dose for using Pegysys monotherapy is set to be 180 micrograms per week for 48 weeks subcutaneously[60].

Many randomized and multicentre analyses were performed to check the efficacy of the coalescent use of Pegysys plus ribavirin and finally approved in 2002[27]. Fried et al, (2001) affirmed the efficacy of combined therapy of Pegysys plus Copegus and showed 46% SVR rates for genotype 1 and 76% for genotypes 2 and 3[50]. Pegylation really helped improve the Overall SVR rates associated with “interferon-based” regimens[21] as shown in the figure 1.

**Optimization strategy for treatment**
Concerning the efficacy of treatment protocol, the dose (interferon and ribavirin) and duration of therapy are kept into considerations. Improved efficacy can be achieved by administering 80% of the interferon dose, 80% of the ribavirin dose, and at least 80% of the standard 48-week duration of therapy. This standard was called as the 80-80-80 rule[25]. It helps to improve adherence with therapy of hepatitis C and eliminate the various side effects associated with therapy[20].

**HEPATITIS C TREATMENT AHEAD OF INTERFERON**
So far, there are no effective vaccines against the HCV and the standard therapy is the combined administration of pegylated IFN and ribavirin (12-72 weeks). But a sustained virological response (SVR) was shown by only 40%-50% of patients infected with HCV genotypes 1 or 4 as compared SVR shown by 80% by individuals infected with genotypes 2 or 3. Moreover, several side effects are associated with the combination therapy[20].

The realization that insight into the viral life cycle will ultimately develop a new approach to treatment of HCV, motivated scientists to successfully design a cell culture system for HCV. For instance the HCV JFH-1 based cell culture system designed in 2005 unraveled various steps in the life cycle of HCV, which promised the development of novel anti-virals against HCV[53,57].

Improved insight into the viral life cycle, favored the development of novel agents beyond interferon, termed as direct-acting antiviral (DAA) agents. These agents were observed to target HCV replication and post-translational processing specifically[48].

**HCV PROTEIN PROCESSING INHIBITORS**
**NS3/4A protease inhibitors**
The NS3/4A protease aids in polyprotein processing by catalyzing the cleavage of the downstream region of genome-encoded polyprotein into 4 functional nonstructural proteins, including the HCV polymerase (NS5B) Therefore, NS3/4A protease has been documented as a key target for anti-HCV therapy[44,48].

Francesco and Carfi (2007) classified protease inhibitors in two major classes on the basis of bonding. The first group is that of non-covalent inhibitors, such as ciluprevir (PI limited due to adverse effects). The second group is represented by covalent reversible inhibitors, also termed as serine-trap inhibitors. Telaprevir (TVR) and boceprevir are the most potent drugs in the later class[50].

**Telaprevir against HCV**
Telaprevir (TVR), a NS3/4A PI, is an orally administered linear keto-amide protease inhibitor studied in monotherapy carried out
Boceprevir is an orally administered peptidomimetic a-ketoamide, which has been tested in three phases of trials for its efficacy against HCV genotype 1. In an initial phase 1 study, 400 mg daily of boceprevir was given in combination with pegylated IFN to patients infected with HCV genotype 1 and who were non-responders to SOC; this type of therapy resulted in an average fall of 2.16 log10 UI/mL viral HCV RNA level in serum, with undetectable HCV RNA levels in 40% individuals within 2 weeks[66-69]. But unfortunately, due to improper dosage of boceprevir (100 mg–400 mg) or an improper dose of boceprevir (800 mg three times a day) with pegylated interferon α-2b without ribavirin, the study resulted in lower overall SVR rates of 2.14%[69].

In January 2006, Schering Corporation initiated a pair of phase II trials for boceprevir called HCV SPRINT-I (Serine Protease Inhibitor Therapy-1) in treatment-naïve patients[70-73]. The results showed that, with triple therapy for 28 weeks, the SVR rates were 54% and a 4-week lead-in treatment with PEG-IFNa-2b/RBV followed by 44 weeks of triple therapy resulted in 75% SVR, as compared with 38% in the control group[66].

Schering Corporation initiated two phase 3 trials named SPRINT-2 and RESPOND-2 for treatment naïve and treatment-experienced patients respectively. Poordad and colleagues trialed 1097 treatment naïve patients having HCV genotype 1 divided into three groups each one receiving a different treatment regimen. All three groups received lead-in treatment with peg-IFN alpha-2b plus ribavirin for 4 weeks. One of the groups, the control group received the SOC for 44 weeks and the 2nd group was treated with boceprevir plus SOC for 24 weeks, while group 3 was treated with boceprevir plus SOC for 44 weeks. SVR rates of 63-66% were observed with boceprevir plus SOC as compared to 38% in SOC (control group) alone[74].

In phase 3 RESPOND-2 trials performed by Bacon and colleagues, 403 previously treated patients were analyzed for treatment boceprevir. HCV RESPOND-2 studies also included a lead-in treatment phase of 4 weeks. SVR rates obtained with RESPOND-2 trials were impressive (59-66%) as compared with the 21% SVR shown by control group[75]. Consequently, the FDA approved the protease inhibitor boceprevir in May, 2011 with the trade name Victrelis for use against HCV genotype 1[76]. The recommended dose is set to be Victrelis (800 mg) administered orally three times daily (every 7-9 hours) with food. Moreover, it is also strongly recommended that Victrelis must be administered in combination with peginterferon Alpha and ribavirin[77].

Some of the most interesting PIs that are tested in phase I and phase-II trials are danoprevir (RG 7227/ITMN191), vanaprevir, MK-7009, BI 201335. These inhibitors are observed to show similar activity against all HCV genotypes and replicon cells. However, they are analogous to which they are analogous.

Boceprevir against HCV

Fig. 2

Telaprevir results in different SVR rate.

For 14 days in patients having HCV genotype 1[80]. TVR therapy demonstrated a spectacular reduction of viral RNA from the replicon cells[81]. Vertex Pharmaceuticals, a global biotechnology company initiated two types of trials in 2006 named, the Protease Inhibition for Viral Evaluation (PROVE-1 and PROVE-2) studies[82,83]. These trials respectively conducted on patients from the United States and Europe, reported the results such that about 67-69% of patients showed sustained virologic response (SVR) in the telaprevir-containing study as compared to the 41-46% SVR rates in patients who received the standard treatment[83,84]. Phase 3 studies, ADVANCE and ILLUMINATE, conducted in about 1500 treatment naïve individuals infected with HCV genotype 1. In the ADVANCE trials, when 6 pills of TVR were given per day along with the SOC (PEG-IFN + RBV) for 12 weeks, 75% SVR was achieved while the SVR was 69% for 8 week regimen. Side effects such as severe rash, itchy skin, anemia, nausea, vomiting, and diarrhea were associated with the therapy. In the ILLUMINATE trials, 6 pills/day of TVR for 24-48 weeks with 12 weeks of triple therapy followed by 8 weeks of PEG-IFN/RBV resulted in overall SVR rates of 72%, while SVR was 92% and 88% at 24 and 48 weeks, respectively for patients who have shown extended Rapid Virological Response (eRVR). eRVR means undetectable HCV RNA at week 4 of treatment and that remains undetectable at week 12. For people who did not have eRVR, SVR after 48 weeks was 64%. It means that no benefits in terms of long duration were obtained in ILLUMINATE study[85].

Another phase 3 study of telaprevir, named REALIZE resulted in SVR rates of 64%, 65% and 17%, respectively when either a 12-week triple combination treatment regimen followed by 36 weeks of SOC was applied, or prior therapy for the 4-week with SOC, followed by triple combination therapy for 12 weeks, and finally therapy with SOC for 32 weeks of treatment-experienced genotype 1 patients or only SOC for 48 weeks[86]. The FDA approved telaprevir with the brand name Incivek very recently in May, 2011 with a recommended dose as the 750 mg telaprevir given as two 375-mg tablets three times daily for 12 weeks[87,88].

Boceprevir against HCV

Boceprevir is an orally administered peptidomimetic a-ketoamide, which has been tested in three phases of trials for its efficacy against HCV serine protease enzyme[89].

In an initial phase 1 study, 400 mg daily of boceprevir was given in combination with pegylated IFN to patients infected with HCV genotype 1 and who were non-responders to SOC; this type of therapy
After a long time of tough and timid research, the sole dominion of interferon seems to be vanishing. Fortunately, after the successful trials of interferon free dose of Gilead’s GS-7977 also called as PSI-7977, a pyrimidine nucleotide analogue, it has been proved that some of the DAAs has a potential role against HCV and can cure HCV up to a great extent without the use of interferon as SOC. Almost 100% SVR rates have been shown with this DAA against genotype 2 and 3[101,102].

Although, the results of phase 3 trials upon an interferon free regimen of GS-7977 formerly called PS-7977 are still awaited that will conclude its efficacy and safety, yet, many recent studies have demonstrated almost 100% efficacy of GS-7977 in combination with Ribavirin and other antivirals like Daclatasvir (NS5A Inhibitor)[103-105].

More such DAAs like the combination of asunaprevir (a protease inhibitor) and Daclatasvir has also shown promising result against HCV without the use of interferon[106,107].

**NOVEL THERAPIES UNDERWAY**

Cyclophilin B Inhibitor as Alisporivir (Debio-025) resulted in a decrease in HCV RNA in patients with genotype 1 or 4[108]. HCV Alpha-Glucosidase Inhibitor such as celgosivir resulted in a greater eVR (Early virological response i.e. 100-times or greater drop in HCV viral load by week 12 of treatment) when applied in combination with SOC for 2 weeks[109]. Furthermore, Immuno-modulatory therapies like Toll-like receptors (TLRs) agonists such as ANA245 (a guanine nucleotide analogue) and human monoclonal antibody as HCV-AB68 resulted in a promising response and are under clinical trials[108,109]. Another novel drug, Nitazoxanide (alinia), a thiazolide, resulted in about 79% SVR rate in treatment naive patients with HCV genotype 4[110]. Nucleic-acid-based antiviral agents as antisense oligonucleotides (mRNA binding fragments), ribozymes (molecular scissors) and, more recently, siRNAs are also being explored as therapeutic agents against HCV[111,112]. Novel interferons such as Hanferon, Interferon 5, Interferon-a-2b XL, Interferon lozenges, Locteron interferon and Albinterferon a-2b (Alb-IFN) are also becoming a part of the HCV pipeline[112]. Spirulina platensis, a cyanobacterium is also under study and has been proved worthy in chronic hepatitis and can be of great use in future[113].

**SUMMARY AND CONCLUSIONS**

After studying the remedial actions of folk medicines, it can be concluded that several of them have a convincing role against HCV but with side effects and less knowledge about their use. Moreover, pegylation improved the value of interferon against and HCV and the use of ribavirin with pegylated interferon added zest to the therapy. Moreover, new strategies beyond “interferon-based” therapies have also proved well in several classes of patients. The most well developed and recently approved direct acting drugs, Telaprevir and Boceprevir are the most promising among DAAs regarding its SVR outcome and safety. However, monotherapy with many DAAs is still not recommended, it indicates that “interferon-based” regimes remains the backbone of therapeutic strategies against HCV. Moreover, most of the DAAs have targeted HCV genotype 1 so far.

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