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Review Article

Emerging therapies in pipeline for chronic hepatitis C

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ABSTRACT

Hepatitis C infection represents a major global public health problem; as it leads to significant morbidity, mortality, and financial burden on healthcare system. According to world health organization, nearly 2- 3% (130-170 million) of the world's population has been infected with hepatitis C. The current standard therapy is limited both in efficacy and tolerability which highlights the large unmet medical need in this area. Recent advances in the understanding of lifecycle of hepatitis C virus and host cell interactions have led to the identification of multiple novel antiviral targets. Intense research effort is currently being directed towards translating these targets into developing more efficacious and safe treatment options for patients living with HCV infection. Current review aims to discuss the emerging therapies in pipeline for chronic hepatitis C outlining their mode of action and current stage of development in clinical trials.

Keywords: Cyclophillin inhibitors, Direct acting antivirals, Hepatitis C, Novel targets, Sofosbuvir

INTRODUCTION

Hepatitis C is prevalent worldwide. For most countries, the prevalence of HCV infection is <3%. For some countries in Asia and Africa prevalence is higher (up to 15%) and highest (>15%) prevalence has been reported in Egypt where the disease is endemic. Causative agent is a positive-strand RNA virus that infects liver and can lead to both acute and chronic hepatitis. Most of acute HCV infections remain asymptomatic and patients are often diagnosed in chronic hepatitis phase. Out of chronically infected individuals 60-70% suffers from chronic liver disease, with as many as 20% developing cirrhosis and 1-5% patients dying as a result of cirrhosis or liver cancer.² Chronic HCV infection has been recently reported as leading cause of liver transplantation and second most common cause of liver cancer worldwide.3-5 economic costs of hepatitis C are enormous as in low prevalence country like US alone, the estimated cost exceeds US\$600 million annually, which is projected to further rise in the coming years.⁶

For the past two decades, standard of care for chronic hepatitis C patients included 24-48 weeks of therapy with

combination of interferon alpha (PEG-IFN α) and ribavirin (RBV). Duration of therapy was based on HCV genotype: 48 weeks for genotypes 1, 4 and 24 weeks for genotypes 2, 3. This dual therapy was capable of inducing sustained virologic response (SVR) in only 40-50% for genotype 1 and up to 70-80% in genotypes 2 and 3 infections.^{7,8} Moreover, it is often poorly tolerated, leading to treatment discontinuation in 10% of the patients while upto 40% of the patients require dose reduction or temporary interruption of PEG-IFN α/RBV.9 Reported adverse events include flu-like symptoms, bone marrow depression, psychiatric symptoms, hemolytic anemia and autoimmune reactions. ¹⁰ Once achieved, an SVR is associated with long-term clearance of HCV infection, which is regarded as a virologic cure, with improved morbidity and mortality. 11-13 Boceprevir and telaprevir, which were approved in Europe and US in 2011 are currently used as a part of triple therapy for genotype 1 HCV infections. Though use of these first generation protease inhibitors in combination with PEG-IFN and RBV, improves effectiveness and increases the cure rate to up to 75% in patients infected with HCV genotype-1, but it is limited by increased incidence of serious adverse events (38-48%), including severe anaemia, liver decompensation and sepsis. 14-17 Anaemia and dysguesia are frequently seen with boceprevir and telaprevir is associated with mild to severe skin rashes. Another limitation is numerous potential drug- drug interactions due to inhibition of CYP450 and P-glycoprotein besides increasing complexity of dosing regimens. 18 Therefore, there is continuing need of newer therapies that promise further improvements in virologic response rate with improved tolerability and reduced duration of therapy. Current review aims to discuss the emerging therapies in pipeline for chronic hepatitis C outlining their mode of action and current stage of development in clinical trials.

Emerging Therapies

According to a recent systematic review there are more than 50 molecules currently in development to treat chronic HCV.¹⁹ These molecules are broadly classified as those that target viral replication directly or those which target host cell proteins that are essential for viral replication. Many drugs targeting viral proteins involved in different steps of viral replication including NS3/NS4A protease, NS5B polymerase and NS5A protein are currently being investigated in clinical trials (as shown in Table 1). Cyclophillin inhibitors and antagomirs on the other hand target host cell proteins. Newer analogues of interferon and ribavirin are also in clinical development.

Table 1: Emerging therapies for the treatment of chronic hepatitis C infection.

Therapeutic classes in development	Direct acting antivirals					Host targeting antivirals	
	NS3/4A protease inhibitor		NS5B polymerase inhibitors		NS5A inhibitors	Cyclophillin inhibitors	Antagomirs
	1 st gen	2 nd gen	Nucleos(t)ide analogue Inhibitors	Non-Nucleoside Inhibitors			
Mechanism of action	Inhibit HCV polyprotein processing and impairs host immune response		Mimic natural substrate of polymerase; get incorporated at the active site of enzyme leading direct chain termination.	conformational change in	Virion	Target host cyclophillin enzyme, which is a functional regulator of HCV replication	Inhibit upregulation of viral RNA by binding to host microRNA- 122
Genotype coverage	Genotype 1	Pan Genotypic	Pan Genotypic	Genotype 1	Pan Genotypic	Pan Genotypic	Genotype 1
Barrier to resistance	Low	High	High	Low	Low	High	High
Advantages	Potent antiviral activity against genotype 1	-Pan- genotypic antiviral activity	-High barrier for resistance -Pan Genotypic	Effective against genotype 1	-Pan Genotypic activity	-Pan Genotypic -High barrier to resistance	High barrier to resistance
Disadvantages	Extensive cross resistance	-	Fewer in pipelin	HCV genotype de dependent -Low barrier to resistance	Low genetic barrier to re resistance	-	-
Molecules in clinical development							
Licensed	Boceprevir Telaprevir	-	-		-	-	-
Phase III	Simeprevir Faldaprevir Asunaprevir	-	Sofosbuvir	-	Daclatasvir	Alisporivir	-
Phase II	Danoprevir Sovaprevir Vaniprevir GS-9256 GS-9451 ABT-450	MK-5172	Mericitabine IDX-184 PSI-7851	791325; ABT-333;	GSK2336805 ABT-267 GS-5885	NIM- 811;SCY-635	Miravirsen

DIRECT ACTING ANTIVIRAL AGENTS

I. NS3/4A protease inhibitors

Non structural NS3/4A serine protease is an important target for antiviral therapy, as it plays two important roles favouring viral replication and persistence in the host. It is essential for post-translational cleavage of the viral genome-encoded polyprotein into mature proteins apart from causing inactivation of cellular proteins required for host immunity against the virus. 20 Protease inhibitors are most advanced agents in terms of clinical development with boceprevir and telaprevir already being used in clinical practice. In general, these agents have potent antiviral activity only against genotype 1 infection and low barrier to resistance as evidenced by rapid selection of resistance variants when used as monotherapy in clinical trials.²¹ Recently in December 2012, FDA announced black box warning on telaprevir use, stating that telaprevir combination treatment must immediately stopped in patients experiencing rash with systemic symptoms or a progressive severe rash.

A number of second generation protease inhibitors with potential advantages of broader genotypic activity, different resistance profiles, improved pharmacokinetics (one to two times daily dosing) and better tolerability are active clinical development.²² These include narlaprevir danoprevir (RG7227), (SCH900518), vaniprevir (MK 7009), sovaprevir (ACH-1625), ABT-450, MK-5172 and GS-9256 in phase II trials. Others for example, Simeprevir, faldaprevir and asunaprevir are currently in phase III trials. 23-27 Simeprevir (TMC 435) is the leading agent; being evaluated in multiple phase III studies (QUEST 1, QUEST 2, PROMISE trials) as oncedaily treatment in combination with pegylated interferon and ribavirin for the treatment of genotype 1 and 4 chronic hepatitis C infection. ²⁸⁻³⁰ Trials evaluating the effect of ritonavir boosting on pharmacokinetic profile of newer protease inhibitors such as danoprevir and narlaprevir are also underway. 31-32

II. NS5B polymerase inhibitors

NS5B polymerase (RNA dependent RNA polymerase) is essential for copying HCV-RNA genome and transcribing mRNA; thus it plays a key role in the synthesis of minus and plus strand viral RNA.³³ Two classes of NS5B polymerase inhibitors –nucleoside and non-nucleoside inhibitors are in development.

a) Nucleos(t)ide analogue inhibitors (NI s): These agents mimic the natural substrates of NS5B polymerase and are incorporated at the active site of the enzyme into the elongated RNA where they act as chain terminators. Since the active site of this polymerase is a highly conserved region of HCV genome, nucleos(t)ide inhibitors have activity against all genotypes. Also NIs

offer high barrier to development of resistance as the NIresistant HCV variants have displayed poor replicative fitness till date. 34,35

Innovator company Gilead sciences has recently filed new drug application to USFDA for approval of sofosbuvir; a once-daily oral nucleotide analogue for the treatment of chronic HCV infection after successful completion of four pivotal phase III trials. Results from studies conducted in treatment-naïve patients with genotype 1, 4, 5 and 6 HCV infections showed sustained virologic response rate of 90% at 12 weeks when sofosbuvir was combined with peginterferon-ribavirin. In treatment naïve patients with genotype 2/3 infection, identical sustained virologic response rate of 67% was observed at end of 12 weeks; when patients were randomly assigned to receive either Sofosbuvir + RBV for 12 weeks or Peg-IFN + RBV for 24 weeks with fewer adverse events in the sofosbuvir group.³⁶ In another placebo controlled trial involving patients with genotype 2/3 infection who were IFN intolerant, SVR at 12 weeks was 78% in those who received Sofosbuvir + RBV for 12 weeks as compared to 0% in placebo group. Another study in treatment experienced patients (genotype 2/3) reported superior response rates with 16 week therapy with sofosbuvir + RBV.³⁷

Mericitabine; an orally administered prodrug of PSI-6130, is another promising agent that has entered phase III trials. In a study, 24-week response-guided combination regimen of mericitabine 1,000 mg twice daily plus peginterferon alfa-2a + ribavirin was found to be well tolerated and more effective than a standard 48-week course of peginterferon alfa-2a + ribavirin.³⁸

b) Non-nucleoside analogue inhibitors (NNIs): These are a heterogeneous group of antiviral compounds that bind to different allosteric enzyme sites, resulting in a conformational protein change before the elongation complex is formed. A number of NNIs such as Setrobuvir (ANA598), BI207127, Filibuvir, VCH-916 Tegobuvir (GS-9190) are currently being evaluated in early phase (I/II) clinical trials. 22,39 These molecules bind to one of the four known NNI binding sites which include benzothiadiazine-(palm 1), benzofuran-(palm 2), a benzimidazole-(thumb 1) and thiophene-(thumb 2) sites.²³ In contrast to NIs, NNIs are not effective across all HCV genotypes. Also these agents have low barrier to resistance as is evidenced by viral breakthroughs in monotherapy studies with NNIs. 40-42 A number of clinical trials evaluating combinations of NNIs with other drug classes such as NS3/4A inhibitors are currently underway.

III. NS5A inhibitors

NS5A protein is involved in various stages of HCV lifecycle. NS5A protein is a part of membrane-bound

replication complex, that catalyses viral replication. It also has a role in assembly and release of virions. Apart from its direct involvement in virus replication, it modulates the cellular environment to favour virus replication and persistence inside the host. ABT-267, GS-5855 are in early phase clinical development. These are highly potent agents that are active against all HCV genotypes but they have a low genetic barrier to resistance.

In treatment naïve patients with HCV genotype 1 infection, daclatasvir based triple therapy resulted in extended rapid virologic response (eRVR) in up to 83% of patients as compared to only 9% patients who received pegIFN-a and ribavirin therapy. Another study reported that when daclatasvir was given as quadruple therapy in combination with asunaprevir, pegylated interferon and ribavirin, it resulted in a high rate of sustained virologic response in genotype 1 prior null responders, making them promising candidates for combination therapies. 45,47 Daclatasvir is currently undergoing phase III trials.

HOST TARGETING ANTIVIRALS

I. Cyclophillin inhibitors

Host cytosolic protein cyclophilin A participates in HCV replication by acting as functional regulator of the NS5B polymerase. 48 Alisporivir; the most advanced agent in clinical development blocks HCV replication by neutralizing the peptidyl-prolylisomerase activity of cyclophilin A. Because it targets the host protein, it has pangenotypic activity. Also it provides a high barrier for development of viral resistance and has an excellent pharmacokinetic and safety profile. 49 Alisporivir has entered phase III development for HCV genotype-1 after promising results in a phase II trial of genotype-1 treatment naïve patients, in which patients who received alisporivir and PEG-IFN/RBV had superior SVR (76%) compared with PEG-IFN/RBV alone (55%).⁵⁰ Alisporivir also has activity against HCV genotypes-2/-3 and IFN-free regimens are being evaluated. 51 FDA has recently ordered clinical hold on the further development of alisporivir due to three cases of severe pancreatitis including one death, though all these cases occurred in patients on combination therapy with alisporivir and interferon.⁵²

SCY-635 is another molecule that has shown potent suppression of HCV replication in studies conducted so far. In a phase 1b multi-dose escalation study, different doses of SCY-635 were given in patients with genotype 1 infection. Mean decline in plasma viral load was 2.24±1.74 log(10) IU/ml after 15 days of therapy with SCY-635 at a dose of 900 mg/day. No dose-limiting clinical or laboratory toxicities were identified. Further post hoc analyses indicated that treatment with SCY-635 increased plasma protein concentrations of various interferons suggesting that restoration of the host innate

immune response to chronic hepatitis C infection may represent another mechanism through which cyclophilin inhibitors exert potent antiviral activity.⁵³

II. Antagomirs

Liver-expressed microRNA-122 is the first identified host miRNA that has been linked to HCV replication. It up regulates viral RNA by binding to two adjacent sites close to the 5' end of HCV RNA.54 Antisense oligonucleotide Miravirsen (SPC3649). promising results in preclinical studies where systemic administration of SPC3649 to chimpanzees chronically infected with HCV induced a long-lasting suppression of viral RNA in serum without the emergence of resistant mutants.55 Results from recently completed phase IIa study which evaluated the safety and efficacy of miravirsen concluded that it led to prolonged dosedependent reductions in HCV RNA levels without evidence of viral resistance.⁵⁶

NEWER ANALOGUES OF CURRENT THERAPIES

A major barrier to successful treatment with current pegylated interferon and ribavirin therapy is the frequent occurrence of adverse events. In clinical trials, approximately 10-15% of treated patients discontinued the therapy due to adverse events; however, in routine clinical practice, the rate of treatment discontinuation has been reported to be much higher. Real world experience report approximately 20% lower SVR rates than those reported in clinical trials. Therefore, effort is being made to develop newer analogues of ribavirin and interferon that have better tolerability than currently available agents.

I. Ribavirin analogues

In an attempt to reduce haematological side effects with ribavirin, ribavirin analogues are being evaluated in clinical trials. One such compound in phase III development is Taribavirin (viramidine). It is a prodrug that gets converted to ribavirin and is selectively concentrated in the liver, thereby reducing uptake by RBCs and less haemolysis.⁵⁹ In a large phase III clinical trial: viramidine safety and efficacy was evaluated against ribavirin (VISER 1). Though taribavirin showed a superior safety profile with anaemia rates being significantly lesser than ribavirin (5% vs 24%) but in terms of efficacy (SVR rates) taribavirin did not meet the criteria for non-inferiority to ribavirin. 60 In another phase 2b randomized controlled trial in 278 treatment-naive patients infected with genotype 1, it was concluded that taribavirin at different doses (20, 25 and 30mg/kg) have efficacy and tolerability comparable to that of weight based ribavirin. Anaemia rates were significantly lower when taribavirin was given at a dose of 20-25 mg/kg as compared to ribavirin.⁶¹ Other ribavirin analogs and IMPDH inhibitors have yielded less promising results and have not advanced further in clinical development.⁵⁹

II. Interferon analogues

Locteron is a slow-release microsphere preparation of recombinant human interferon alpha 2b that needs to be administered once every 2 weeks as compared to weekly injections of pegylated interferon.⁶² Results of a 12 week open-label, randomized trial of locteron in 32 patients of chronic HCV genotype 1 infection concluded that treatment was well tolerated, with 97% patients successfully completing the treatment. Flu-like symptoms were generally mild and brief. 63 PEG-IFN-lambda is another promising analogue that is active against all HCV genotypes. A phase II study demonstrated that it causes less marrow toxicity and flu-like symptoms and leads to improved rapid virological response.⁶⁴ Two large phase III studies of Albinterferon alfa-2b in patients with HCV genotype 1 found that it was neither superior in efficacy nor in tolerability to pegylated interferon. Based on the risk/ benefit ratio, the approval of Albinterferon alfa-2b has been recently suspended. 65,66

CONCLUSION

Novel standard of care i.e. triple therapy itself represents a milestone in the management of chronic HCV infection. But recent insights into lifecycle of HCV and host cell interactions have definitely opened up new avenues of research with multiple novel drug targets. Most of the agents have shown great promise in clinical trials so far, but therapeutic potential of these molecules needs to be seen in the future when the drugs are used in larger number of people; as phase III trials are done under controlled conditions in highly selected subset of patients. Nevertheless, it seems that combination therapies with direct acting antiviral agents do hold a promise for future in chronic HCV management.

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