The Present And Emerging Investigational Drugs For Chronic Hepatitis C: Current Status

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Citation
R Kumar. The Present And Emerging Investigational Drugs For Chronic Hepatitis C: Current Status. The Internet Journal of Pharmacology. 2008 Volume 6 Number 2.

Abstract
Chronic hepatitis C is caused by flavi virus (RNA virus) and is the leading cause for cirrhosis, hepatocellular carcinoma and liver transplantation. The standard therapy of chronic hepatitis C is peg interferon α weekly plus oral-ribavirin daily is not effective in all patients and is limited by adverse effect. Therefore new investigational drugs are being developed and in pipeline. This article focuses on new investigational drugs that are presently in an advance stage of development also focuses on newer interferons, ribavirin analogue and anti apoptotic drug.

INTRODUCTION
Viruses are obligate intracellular parasites, their replication depends on synthetic processes of the host cell. Hepatitis C caused by RNA flavi virus, 80% of individual will become chronically infected. Chronic hepatitis C is the leading cause for cirrhosis, hepatocellular carcinoma and liver transplantation.

The goal of therapy patients with chronic hepatitis C is viral eradication and primary efficacy and point of treatment is achievement of SVR (Sustained Viral Response). SVR defined as the absence of detectable viremia for 6 months after completion of treatment. Sustained viral response is associated with improvement in liver pathology and reduction in risk of cirrhosis and hepatocellular carcinoma.

The standard treatment in patients with chronic hepatitis C infection is once weekly pegylated interferon alpha with oral ribavirin (a synthetic nucleotide analogue) daily. Combination therapy is more effective than monotherapy with interferon. Therefore monotherapy with pegylated interferon alpha is indicated in patients with chronic hepatitis C infection who can not tolerate oral ribavirin. Side effects with the use of interferon alfa include dose dependent hemolytic anaemia, depression, instability, cough and insomnia.

Currently available therapy for patient with chronic hepatitis C provides a cure rate of 40-90% and associated with significant adverse effects that often necessitate discontinuation. Therefore new drugs with higher efficacy and better tolerability are needed.

The availability of a full length HCV genome has enabled the identification of new targets and facilitates screening of new anti HCV drug. Several targets have been identified in HCV genome for anti HCV drug, including IRES (Internal Ribosome Entry Site), E1/E2 (Envelop glycoprotein), P7 NS2, NS3, NS5 and NS5B. Many specifically targeted small molecule inhibitors are being developed and are emerging, future drug for patient with chronic hepatitis C infection.

This article focuses on emerging future anti-HCV drugs that are currently in clinical trial and in advance stage of development.

INVESTIGATIONAL NEW DRUGS (IND)
NS3/4A SERINE PROTEASE INHIBITOR
Telaprevir (VX-950) (Manufactured by vertex) is a peptidomimetic inhibitor of NS3/4A protease. In a phase-Ib trial (nonresponders to previous antiviral therapy) telaprevir monotherapy reduced HCV RNA rapidly by 3.5 – 4.8 log in a dose dependent manner ( in this trial patients were treated for 14 days with Telaprevir at three different doses. 450mg
every 8 hours, 750mg every 8 hours or 250mg every 12 hours or with placebo). Mild gastrointestinal symptoms were noted in patient with telaprevir therapy.

The combination treatment with telaprevir plus peginterferon-α-2a reduced the HCV RNA by 5.5 log after 14 days in previously untreated patients with chronic hepatitis C genotype-I. Combination therapy causes more reduction in HCV RNA indicating additive effect of telaprevir with peginterferon-α-2a. HCV mutant resistant to telaprevir remained sensitive to peginterferon-α-2a. The triple combination treatment with telaprevir, peginterferon-α-2a and ribavirin in the PROVE trials (Phase II trials) yielded good results. At the EASL (European Association for the Study of the Liver) 2008 meeting in Milan, Italy, final results of the PROVE trials recently became available, both PROVE 1 and PROVE 2 trials had shown that the telaprevir based (triple combination) regimen resulted in a 20% higher SVR than previously achieved with standard treatment with peginterferon plus ribavirin in patients with chronic hepatitis C. Adverse effect with telaprevir therapy were rash and anaemia.

Boceprevir (SCH 503034): Similar to telaprevir is peptidomimetic NS3/4 protease inhibitor (manufactured by shering–Plough) Boceprevir based regimen revealed an additive effect over peginterferon-α-2b in a phase 1b study, in patient with chronic hepatitis C genotype-I (nonresponders to previous peginterferon-α-2b plus ribavirin therapy). In an ongoing phase-II trial (SPRINT–I study) interim result were presented as abstract at the EASL 2008 meeting. It suggest that triple combination treatment with boceprevir, peginterferon-α-2b and ribavirin in treatment naïve HCV genotype-I patient resulted in an early virologic response than therapy with peginterferon plus ribavirin. The boceprevir based treatment was associated with gastrointestinal discomfort, anaemia and dyspepsia as adverse effect.

TMC45350 – (manufactured by tibotec) a protease inhibitor is presently in an ongoing phase-I trial showed a reduction in HCV RNA and well tolerated.

NS5A inhibitor A-831, (manufactured by arrow therapeutic) NS5A, a non-structured protein essential for hepatitis C virus replication. A831 inhibit NS5A protein in HCV and exert antiviral activity currently being studied in phase-I trial.

NS5B polymerase inhibitor: R1626 is a prodrug of the ‘4’-azidocytidine, a nucleoside analogue (manufactured by Roche). R1626 showed greatest viral blood reduction in a multi-dose study (phase-Ib trial) in patients with chronic hepatitis C genotype-I. In a phase-IIa study R1626 with peginterferon plus ribavirin (triple combination treatment) resulted 5.2 log decline in HCV RNA showing robust synergistic antiviral effect and the antiviral effect was sustained. Haematological adverse effects were observed.

R7128 is a prodrug, a nucleoside analogue NS5B polymerase inhibitor (manufactured by Roche). R7128 in a phase-I trial, following multiple, ascending, oral doses showed antiviral effects in patients with HCV genotype-I infection, who have failed with prior interferon therapy, headache was the most common adverse events. R7128 in triple combination with peginterferon and ribavirin the early result showed synergistic effect similar to R1626.

Non-nucleoside analogue NS5B polymerase inhibitor-BILB1941 (manufactured by Boehringer ingelheim) BILB1941 in a phase-I trial showed antiviral activity after 5 days treatment, in patient with chronic hepatitis C genotype-I but gastrointestinal adverse effect are limiting factor.

GS9190 (manufactured by Gilead) in a phase-I trial and interim result showed antiviral effect ie decline HCV-RNA and doses which was well tolerated.

Cyclophelin Inhibitor: Cyclophelin are intracellular protein and are involved in protein folding, serve as cofactor of the NS5B RNA dependent RNA polymerase.

DEBIO-025 (manufactured by Debiopharm) the cyclophelin inhibitor has dual anti HCV and anti HCV activity. In a phase-I trial DEBIO-025 was administered in HIV/HCV coinfected patients showed antiviral effect (ie. Decline in HIV-I viral load and decline in HCV RNA).

CURRENTLY AVAILABLE THERAPY FOR HEPATITIS C INFECTION-INTERFERONS

Interferons are host cytokine proteins that exhibits antiviral, immunomodulatory and anti-proliferate activity. Interferons are grouped into three families IFN-α, IFN-β and IFN-γ. The IFN-α, IFN-β families comprise type-I IFN, ie. acid stable proteins induced by viral infection and act on same receptor on target cell. IFN-γ-a type-II IFN is acid labile product of activated T lymphocyte and act on separate receptor on target cells. IFN-γ approved for use in hepatitis C infection and act by inducing intracellular signal, following binding with specific cell membrane receptor resulting in inhibition.
of viral penetration, translation, transcription, protein processing, maturation and release as well as increased expression of major histo-compatibility complex antigen enhanced phagocytic activity of macrophages and augmentation of the proliferation and survival of cytotoxic T cell.

Interferon-α-2a and interferon-α-2b are currently available for treatment of hepatitis C virus infection administered subcutaneously or intramuscularly, elimination half life is 2-5 hours and need to be administered daily or 3 times weekly.

Pegylated interferon-α is a fusion molecule of polyethylene glycol molecule and interferon-α. Pegylated interferon α-2a and pegylated interferon α-2b need to be administered once weekly because of slower clearance of these drug result in longer terminal half life allowing for less frequent dosing.

NEWER INTERFERONS IN DEVELOPMENT

Albinterferon-α-2b: Albumin–interferon-α-2b (Albinterferon-α-2b) is a fusion molecule of interferon-α-2b and human serum albumin, this result an extended half life of 150 hours, allowing less frequent administration, albinterferon-α-2b administered every 2-4 week. Albinterferon-α-2b exhibit dose dependent antiviral activity both in non-responder and treatment naïve patients with chronic hepatitis C genotype I.

Omega Interferon: New drug delivery system – design to provide continuous drugs delivery by an implantable device. Omega interferon in a phase-II trial showed antiviral efficacy administered with or without ribavirin in patient with chronic hepatitis C genotype-I.

Recombinant interferon-β-2b – The controlled release lemmata derived interferon-β-2b (Loceteron™). The interferon-β-2b attached to biodegradable microsphere providing slow release of interferon-β-2b, allowing administration every 2 week interval. Loceteron with ribavirin in a phase-IIa trial showed antiviral efficacy with better safety and tolerability profile.

RIBAVIRIN ANALOGUE

Taribavirin – (Viramidine) is a prodrug of ribavirin, converted to ribavirin in liver. The advantage with taribavirin is that the haemolytic anaemia which is the main adverse effect associated with ribavirin is minimum, as taribavirin does not significantly accumulated in RBCs. Taribavirin with peginterferon-β-2a in a phase-II trial study showed similar antiviral effect and significantly less haemolytic anaemia than ribavirin.

Other Investigational New Drugs (IND) - Toll like receptor agonist Resiquimod. Toll like receptor (TLRs) identify the presence of invading microorganism and initiate production of proinflammation cytokines and chemokines. Resiquimod through TLRs initiate induction of cytokines, interferon-α, interleukin 12 and TNF-α, oral resiquimod in a phase-IIa study showed a antiviral effect.

Tumor Necrosis Factor Antagonist – Etaercept as an adjuvant to interferon and ribavirin, in a phase - II study showed on treatment virological response and attenuation of adverse effect in patient with chronic hepatitis C infection.

IMPDH Inhibitor – Merimepodib – IMPDH is inosine 5’ monophosphate dehydrogenase, catalysis the biosynthesis of guanine nucleotide. Merimepodib is non competitive inhibitor of IMPDH, in a phase-II study merimepodib with peginterferon β-2b and ribavirin showed on treatment virological response in nonresponders to previous therapy.

INVESTIGATIONAL DRUG THAT REDUCES HEPATIC FIBROSIS:

Antiapptotic caspase inhibitor–IDN6556: Pockron PJ et al reported that IDN6556 may lower aminotransferase levels in patient with chronic hepatitis C infection and may reduce hepatitis C fibrosis.

Investigational drugs that have showed good antiviral effect in clinical trials in patient with chronic hepatitis C infection but further development has been stopped due to toxicity includes.

Ribozymes RPI13919 – was in a phase-II trial, halted due to severe toxicity in primates. Antisenseoligonucleotides ISIS14803 – was in a phase-I trials, halted due to ALT level >10 times the upper limit of normal in patients.

NS3/4A protease inhibitor ciluprevir (BILN2061) – was in a phase-I trials, halted because of cardiac toxicity in animals.

GS-9132 – was in a phase-I trial, halted because of nephro toxicity in patients.

Valopicitabine (NM283) (a nucleoside analogue) NS5B-RNA polymerase inhibitor - was in a phase-I trial, halted due
to severe gastric toxicity appear also ribavirin antagonizes the activity of valopicitabine (Invitro studies) .

CONCLUSION

Chronic hepatitis C is manageable disease the current treatment is peginterferon-α weekly plus oral ribavirin daily but this is not 100% effective (cure rate is 40% to 90%) also the adverse effects are the limiting factors. New specific anti-HCV investigational drugs are in pipeline and in development.

Adding a new specifically targeted antiviral therapy on to peginterferon-α plus ribavirin standard treatment is the most promising strategy. Resistance due to mutation i.e. HCV polymerase develops early limits the efficacy of investigational drugs. Combination of different antiviral drugs may reduce the development of resistance. Anti-apoptotic inhibitor like caspase inhibitor may improve hepatic fibrosis. Optimal combination of drugs that result in-sustained viral response, reduce hepatic fibrosis, reduces adverse effects or better tolerability will be the more effective treatment.

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