Review Article

Update of old and emerging therapies in chronic hepatitis C

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Abstract

The main aim in treating hepatitis C virus (HCV) infection is to achieve a sustained virological response (SVR). It is defined as undetectable HCV-RNA in peripheral blood 24 weeks after the end of treatment. The RNA is detected by polymerase chain reaction (PCR) technique. The SVR practically reflects eradication of HCV infection and cure of the underlying HCV-induced liver disease.

Treatment of HCV-induced chronic hepatitis includes one of the available Interferon-α (INF-α) in combination with Ribavirin (RBV). To achieve much better results, combination of PEG-INF with RBV is currently recommended. This regimen is quite effective in treating HCV genotype 2 and 3 but much less so in genotypes 1 and 4. At the same time it has long been observed that these combinations have sometimes severe side effects and contraindications limiting their efficacy and applicability in a significant number of chronic HCV patients. Therefore, the importance of improving existing therapies and developing new, effective, safe and tolerable drugs is well appreciated, worldwide. This review describes improvements in the current standard therapy and new emerging drugs.

Keywords: HCV, SVR, PEG-INF, STAT-C.

Introduction

The agent causing post transfusion hepatitis not due to hepatitis A or B viruses (non-A, non-B hepatitis) was detected and named as HCV in 1988.[1,2]

HCV infects about 170 million persons worldwide. HCV infection remains one of the most common cause of chronic hepatitis and cirrhosis and a predisposing factor for hepatocellular carcinoma.

Since the successful use of INF-α in treatment of chronic HCV hepatitis in 1989[3] new drugs are constantly being evolved. Higher rate of success have been achieved, using combination of INF-α and RBV. Further success was attained with PEG-INF combined with RBV. Recently an oral combination therapy has shown promising results which may lead to interferon free treatment of chronic HCV hepatitis.[4]

In this article, existing therapies with recent improvements and development of new emerging drugs in clinical development phases will concisely be reviewed with reference to individual groups (Table).

Table: Groups of Anti HCV agents in present use and under trials.

Groups	In Present Use	Newly Emerging
Recombinant Interferons (INF)	INF-α2a INF- α2b PEG-INFα2a PEG-INFα2b	Albuferon Locteron Peginterferon-λ Consensus-INF(CIFN)
Nucleoside analogues	Ribavirin	Viramidine (Taribavirin)
Protease inhibitors	NONE	Telaprevir (VX-950) Danoprevir(ITMN191) Boceprevir
RNA- Polymerase Inhibitors		
a: Nucleoside analogues	NONE	Valopicitabine R1626 RG7128
b: Non-nucleoside analogue		HCV796
Cyclophilin binders	None	Cyclosporin-A NIM811 DEBIO-025
Immunomodulating agents		
a:Immunoglobulin	None	Hyperimmune AntiHC Immunoglobulin
b: Toll-like receptor agonists		CPG-10101
Caspase inhibitors	None	PF-03491390

Interferons:

Interferons are natural cellular proteins with variable actions such as direct antiviral effect, induction of cytokine secretion, recruitment of immune effector cells and induction of cell differentiation. Several different types of interferon are approved for use in humans.

In 1980 recombinant DNA technology was used to produce yeast derived INF α2a[5] Although the short courses of standard IFN monotherapy, first introduced in the 1980s by Hoofnagle et al,[6] Davis et al,[3] and Di Bisceglie et al[7] showed sustained improvement in liver disease and loss of virus in less than 10% of patients, these therapies were the first to cure chronic viral hepatitis. A major advance in the treatment of chronic hepatitis C was the addition of the oral nucleoside analogue ribavirin to the IFN regimen. In 1998, McHutchison et al[8] and Poynard et al,[9] reported that IFN alfa-2b and ribavirin in combination therapy used for 6-12 months

resulted in sustained eradication rates of 30-40%. However, patients with HCV genotype 1 who were treated for 12 months had a much less favourable response to therapy with IFN and ribavirin compared with patients infected with genotypes 2 and 3, in whom a 6-month course of therapy was sufficient.

Developments in IFN technology led to the development of long-lasting IFNs in which Polyethylene Glycol (PEG) molecules were added to IFN. These new PEG-IFNs have better sustained absorption, a slower rate of clearance, and a longer half-life than those of unmodified IFN. They allow more convenient once-weekly dosing. The addition of ribavirin to PEG-IFN heralded a new era in the treatment of chronic HCV. In January 2001 Food and Drug Administration (FDA) approved the use of PEG-INFα in the USA. Current standard therapy for HCV includes PEG-IFN in combination with ribavirin, and this combination is effective in approximately 40-50% of genotype 1-infected patients and 80% of genotype 2 and 3-infected patients.[10]

Albinterferon (Albuferon) is a genetic fusion polypeptide of albumin and interferon alfa-2b with a longer half life than pegylated interferons. It can be dosed once every 2 or even 4 weeks. Recent studies have indicated that albinterferon alfa-2b is not better tolerated than peginterferon alfa-2a.[11]

Locteron is a controlled-release interferon alfa-2b which is injected every 2 weeks. In a short term study, controlled release interferon alfa-2b showed less flu like symptoms than peginterferon alfa-2b injected every week indicating that the controlled-release formulation may have a better tolerability. Larger trials powered to examine adverse event profiles and antiviral activity are being initiated.[12]

Peginterferon-λ is a pegylated type III interferon that binds to a unique receptor with more limited distribution than the type-I interferon receptor. Peginterferon-λ is currently investigated in combination with ribavirin.[13]

Consensus interferon (CIFN) is a recombinant type 1 IFN containing 166 amino acids. CIFN was derived by scanning the sequences of several natural alpha IFNs and assigning the most frequently observed amino acid at each corresponding position.The "DIRECT" trial suggested some benefit.[14] The efficacy of daily dosing of CIFN with either gamma interferon and/or RBV in 60 treatment-naive patients with genotype 1 chronic hepatitis C has also been evaluated and reported in 2005.[15] The authors suggested that gamma IFN may be an effective supplement for RBV or additive in IFNα/RBV therapy specially for difficult-to-treat genotype 1/high viral load patients or patients with bad tolerability or contraindications for RBV.

Overall, the new interferons may improve convenience and tolerability of interferon based therapy. However, the current results on viral efficacy indicate that response rates will not be improved by the new interferons.

Nucleoside Analogues:

Ribavirin:

The mechanism of action of RBV in HCV therapy is not well known. RBV seems to render the HCV particles less infectious. Since the landmark studies in 1998, RBV has been successfully used in combination with INF to treat chronic HCV infection.[8,9]

Alternatives to Ribavirin:

Viramidine (Valeant Pharmaceuticals, also referred as Taribavirin), is a pro-drug of RBV, which is converted to RBV in the liver and does not significantly accumulate in erythrocytes. It was designed to overcome the haemolytic anaemia which is RBVs major side-effect. Results of recent studies have made it obvious that viramidine is superior to the currently used RBV in terms of anaemia but clearly inferior in terms of efficacy.[16] Therefore, higher (weight based) viramidine doses or other compounds have to be tested now in comparison with RBV.

Specifically targeted antiviral therapy for HCV (STAT-C):

Major research efforts are ongoing in the development of 'Specifically Targeted Antiviral Therapy for HCV' (STAT-C). Based on the best knowledge of the molecular structure of the HCV, its component proteins, and the various phases of the replication cycle of the virus, specific small molecules, inhibitors of the viral enzymes have been developed.

Hepatitis C virus is a single-stranded RNA virus whose proteins are coded by a single open reading frame. The resultant polyprotein is cleaved into smaller proteins by different enzymes.

The HCV protease produced from the NS3 region of the genome has been isolated and its tertiary structure determined by X-ray crystallography to recognize specific molecular target sites promising for future NS3 protease inhibitor therapies.

The structure of the helicase molecule has similarly been determined. Although the NS3 helicase has been considered in the past to be a potential target for anti-HCV drugs, attempts to develop specific helicase inhibitors have met with failure.

Other portions of the HCV genome that make potential antiviral targets include the internal ribosomal entry site (IRES) located in the 5' noncoding region of the genome which is the most attractive target for ribozymes and antisense oligonucleotides. Unfortunately studies with the

ribozyme RPI-13919 (heptazyme) and the antisense oligonucleotide ISIS1-4803 were interrupted because of adverse effects and limited efficacy.

Another area of interest in HCV genome for STAT-C is the RNA-dependent RNA polymerase of the virus.

NS3-4A protease inhibitors:

The NS3-4A protease is a member of the chymotrypsin serine protease family generating components of the viral RNA replication complex by cleaving the nonstructural region of the viral polyprotein. A few groups of specific inhibitors of this enzyme have been developed.

The first protease inhibitor which had entered in clinical trials was the BILN-2061(Ciluprevir).[17] Unfortunately, the trials were halted because cardiac toxicity was observed in laboratory animals. Moreover, mutations conferring resistance to this drug have also been described.

VX-950 or Telaprevir (Vertex Pharmaceuticals, USA) is another peptidomimetic HCV protease inhibitor that has shown strong antiviral activity in small studies, both alone and in combination with Peg-IFN. Telaprevir in combination with PEG-INF and RBV has shown significant benefit in PROVE 1 and 2 trials.[18,19] Furthermore PROVE 3 trial[20] has shown superior SVR to triple therapy (Telaprevir+PEG-INFα2a+RBV) in HCV genotype-I non responders. Overall, the studies provide evidence that protease inhibitors added to the standard combination regimen will be a treatment option for patients who failed previous antiviral therapy.

Boceprevir, another NS3/4A serine protease inhibitor, binds reversibly to the NS3 protease active site and has potent anti HCV activity alone and in combination with interferon alfa-2b. SPRINT-1 study assessing safety and efficacy of boceprevir in combination with peginterferon alfa-2b (1.5 μg/kg/week) and ribavirin in treatment naïve patients with chronic hepatitis C genotype 1 infection were presented in 2009.[21]

The results from the PROVE and the SPRINT-1 trials confirm the concept that specific protease inhibitors are able to improve the cure rates of patients with chronic hepatitis C. Furthermore, both trials indicate that ribavirin is still highly necessary for achieving a sustained virologic response (SVR).

Danoprevir (ITMN191) another HCV protease inhibitor has been shown to be effective in combination therapy against HCV infection. Recently, INFORM-1, a short term phase-1 study has shown that Danoprevir in combination with a nucleoside polymerase inhibitor (RG 7128), both used orally are able to suppress HCV replication without RBV or INF. The authors suggest that it may hold promise for an interferon free mode of treatment for HCV in future.[4]

New protease inhibitors:

SCH 900518 (Narlaprevir), TMC435, BI201335 and MK-7009 are novel NS3/4A protease inhibitors currently in clinical trials.

RNA Dependent RNA Polymerase Inhibitors:

Another very attractive drug target is the HCV-RNA-dependent RNA polymerase. It can be inhibited either by nucleoside, nucleotide analogues or by non-nucleoside analogues.

Nucleoside analogues:

Valopicitabine (NM283) was the first nucleoside analogue polymerase inhibitors tested in patients with chronic hepatitis C. The development of valopicitabine was stopped due to gastrointestinal adverse events which were severe in some patients.[22] Another nucleoside analogue R1479 (4'-azidocytidine) is a potent inhibitor of NS5B dependent RNA synthesis and hepatitis C virus replication in cell culture. R1626 is a prodrug of R1479.[23] Despite promising results development of R1626 was stopped due to severe neutropenia.

R7128 is another nucleoside analogue NS5B polymerase inhibitor, INFORM-1 trial has suggested its promising future.[4]

Nucleotide Analogue:

IDX184 is a liver-targeted nucleotide prodrug designed to enhance formation of its active triphosphate in the liver while minimizing systemic exposure of the parent drug and its nucleoside metabolite.[24] Clinical data are awaited.

Non-nucleoside Analogues:

The non-nucleoside polymerase inhibitors are drugs which bind allosterically on the enzyme surface near to its active site to disturb its structure and function.

HCV-796 is a non-nucleoside polymerase inhibitor that has demonstrated potent antiviral activity in vitro and in patients with chronic hepatitis C. Its clinical development was discontinued in the phase 2 programme.[25]

Recently, data from several new non-nucleoside polymerase inhibitors were presented. The development of filibuvir (PF 00868554) is most advanced.[26] Filibuvir is currently investigated in combination with peginterferon alfa-2a and ribavirin. The non-nucleoside polymerase inhibitors VCH-916, ANA598, BI 207127 and VCH-222 were investigated only in monotherapy so far. Some of them are being evaluated in combination with other anti HCV agents as well.

Inhibitors targeting Host cell Proteins:

Cyclophilin-inhibitors:

Cyclophilins are ubiquitous proteins in human cells that are involved in protein folding. They also participate in HCV replication. It was shown that cyclophilin B binds to the HCV NS5B polymerase and stimulates its RNA-binding activity. Cyclophilin inhibitors show strong antiviral activity in vitro and in vivo.

The cyclophilin inhibitor DEBIO-025 and NIM811 another oral non-immunosuppressive cyclophilin Inhibitor are being evaluated with encouraging preliminary results.[27,28] SCY-635 is a non-immunosuppressive analogue of cyclosporine A that exhibits potent suppression of HCV RNA replication in vitro.[29] SCY 635 binds to human cyclophilin A.

Silibinin another cyclophilin inhibitor is widely used orally for treatment of hepatitisC, but its efficacy is unclear. Intravenous silibinin was investigated in non-responders to prior interferon-based antiviral therapy and showed a significant decline in HCV RNA. Results are still pending.[30]

Nitazoxanide:

Nitazoxanide is a thiazolide anti-infective with activity against a number of protozoa, bacteria, and viruses. It is FDA approved for treatment of cryptosporidium and giardia. Nitazoxanide inhibits replication of hepatitis C virus, hepatitis B virus, and rotavirus in vitro. The mechanism of action is thought to be likely through cellular processes rather than specific anti viral targets. Studies suggest that nitazoxanide may have antiviral activity in all types of HCV specially in combination with PEG-INF and RBV.[31]

Immune Therapies - Immunomodulatory Agents:

The critical role of innate as well as adaptive immunity has been reported in HCV persistence and liver injury. There are many attempts in developing new immunomodulatory agents in HCV treatment such as hyperimmune anti-HCV immunoglobulins, therapeutic vaccines (monoclonal antibody against a linear epitope of HCV E2 glycoprotein MBL-HCV1 that neutralizes pseudoviruses from multiple HCV genotypes).[32,33] But most of them have demonstrated questionable efficacy until now. Presently the most challenging and promising therapeutic agents in development are the agonists of the Toll-like receptors (TLR).

CPG-10101 (Actilon™, COLEY Pharmaceutical Group, USA) is an investigational, synthetic TLR9 agonist being developed as an antiviral and enhancer drug for treatment of chronic HCV infection. It is a short synthetic oligonucleotide which binds to TLR9 receptors on human B cells and plasmacytoid dendritic cells, inducing Th1 immune responses such as production of tumour necrosis factor, interleukin-12 (IL-12) and IFN-α together with stimulation of B-cell proliferation and antibody production. Preliminary reports are encouraging.[34]

Ongoing clinical trial of ANA245(Isatoribine) and its oral prodrug ANA975 a guanosine analogue TLR7 agonist was suspended for safety reasons (July 2007) because of informations obtained from preclinical toxicology studies confirming intense immune stimulation in animals.

Caspase Inhibitors:

Caspases are a family of cystein proteases. They increase rates of hepatocyte apoptosis and activated caspases have been observed in viral hepatitis C. Inhibiting caspases with a specific pancaspase inhibitor may play an important role in HCV treatment. A recent study examined the efficacy and safety of the pancaspase inhibitor PF-03491390 in reducing elevated ALT and AST in patients with chronic HCV infection.35 It needs further evaluation

Conclusion

According to recent estimates, hepatitis C has become a worldwide health problem, affecting millions of people in the world. Recently, standard combination therapy with Peg-IFN and RBV aiming at eradication of the HCV has a relative limited efficacy specially in specific subgroups of patients. In order to improve treatment success, novel drugs and new combinations of therapies are gaining ground in treating hepatitis C patients. The success of the ideal new potent anti-HCV drug candidate depends on its ability to suppress the virus together with its ability to prevent the development of resistant viral strains and least possible adverse effects.

The sustained virologic response rates (SVR) have not substantially been improved since the introduction of PEG-INFs-2a/-b plus ribavirin. Recent studies with the HCV specific protease inhibitors telaprevir and boceprevir convincingly demonstrated that two major goals of antiviral therapy (i) higher sustained virologic response rates and (ii) shorter treatment duration in patients infected with HCV genotype 1 can be achieved when HCV-specific inhibitors are combined with standard combination therapy (PEG-INF with RBV). Data from the pivotal phase 3 trials are awaited before triple therapy with telaprevir or boceprevir with peginterferon/ribavirin can become the new standard of care.

Preliminary results on the combination of a protease and a polymerase inhibitor, HOME-1 trial indicates good tolerability and additive antiviral activity in patients with chronic hepatitis C. The ultimate goal of antiviral therapy achieving HCV eradication without peginterferon/ribavirin still remains a question, although appears to be attainable in near future.

References

1. Choo QL, Kuo G, Weiner AJ, Overby LR, Bradley DW, Houghton M. Isolation of a cDNA clone derived from a blood-borne non-A, non-B viral hepatitis genome. Science 1989; 244: 359-62.
2. Kuo G, Choo QL, Alter HJ, Gitnick GL, Redeker AG, Purcell RH, et al. An assay for circulating antibodies to a major etiologic virus of human non-A, non-B hepatitis. Science 1989; 244: 362-4.
3. Davis GL, Balart LA, Schiff ER, Lindsay K, Bodenheimer HC Jr, Perrillo RP, et al. Treatment of chronic hepatitis C with recombinant interferon alfa. A multicenter randomized, controlled trial. Hepatitis Interventional Therapy Group. N Engl J Med 1989; 321: 1501-6.
4. Gane EJ, Roberts SK, Stedman CA, Angus PW, Ritchie B, Elston R, et al. Oral combination therapy with a nucleoside polymerase inhibitor(RG 7128) and danoprevir for chronic hepatitis C genotype 1 infection(INFORM-1): a randomized, double blind, plcebo controlled, dose escalation trial. Lancet 2010; 376: 1467-75.
5. Nagata S, Taira H, Hall A, Johnsrud L, Streuli M, Ecsödi J, et al. Synthesis in E. coli of a polypeptide with human leukocyte interferon activity. Nature 1980; 284: 316-20
6. Hoofnagle JH, Mullen KD, Jones DB, Rustgi V, Di Bisceglie A, Peters M, et al. Treatment of chronic non-A,non-B hepatitis with recombinant human alpha interferon. A preliminary report. N Engl J Med 1986; 315: 1575-8.
7. Di Bisceglie AM, Martin P, Kassianides C, Lisker-Melman M, Murray L, Waggoner J, et al. Recombinant interferon alfa therapy for chronic hepatitis C. A randomized, double-blind, placebo-controlled trial. N Engl J Med 1989; 321: 1506-10.
8. McHutchison JG, Gordon SC, Schiff ER, Shiffman ML, Lee WM, Rustgi VK, et al. Interferon alfa-2b alone or in combination with ribavirin as initial treatment for chronic hepatitis C. Hepatitis Interventional Therapy Group. N Engl J Med 1998; 339: 1485-92.
9. Poynard T, Marcellin P, Lee SS, Niederau C, Minuk GS, Ideo G, et al. Randomised trial of interferon alpha2b plus ribavirin for 48 weeks or for 24 weeks versus interferon alpha2b plus placebo for 48 weeks for treatment of chronic infection with hepatitis C virus. International Hepatitis Interventional Therapy Group (IHIT). Lancet 1998; 352: 1426-32.
10. Fried MW, Shiffman ML, Reddy KR, Smith C, Marinos G, Gonçales FL Jr, et al. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. N Engl J Med 2002; 347: 975-82.
11. Nelson D, Benhamou Y, Chuang WL, Lawitz E, Flisiak R, Rodriguez-Torres M, et al. Efficacy and safety results of albinterferon alfa-2b in combination with ribavirin in interferon alfa treatment naive patients with genotype 2 or 3 chronic hepatitis. J Hepatol 2009; 50S: 378.
12. Lawitz E, Younossi ZM, Shiffman ML, Gordon S, Ghalib RH, Long W, et al. Randomized trial comparing systemic and local reactions to controlled-release interferon alfa-2b and pegylated interferon alfa-2b in hepatitis C patients who failed prior treatment. J Hepatol 2009; 50S: 231.
13. Shiffman ML, Lawitz E, Zaman A, Vierling J, Yoffe B, Freeman J, et al. Peg-IFN-l: Antiviral activity and safety profile in a 4- week phase 1b study in relapsed genotype 1 hepatitis C infection. J Hepatol 2009; 50S: 237.
14. Bacon BR, Shiffman ML, Mendes F, Ghalib R, Hassanein T, Morelli G, et al. Retreating chronic hepatitis C with daily interferon alfacon-1/ribavarin after non-response to pegylated interferon/ribavarin: DIRECT results. Hepatology 2009; 49: 1838-46.
15. Kaiser S, Hass H, Gregor M. Consensus Interferon in combination with gamma interferon and/or ribavirin leads to a significant response in treatment-naive hepatitis C genotype 1 patients. Abstract 66839. 56th Annual Meeting of the American Association for the Study of Liver Diseases (56th AASLD), San Francisco, CA, 2005.
16. Benhamou Y, Pockros P, Rodrieuez-Torres M, Gordon S, Shiffinan M, Lurie Y, et al. The safety and efficacy of VIRAMIDINE® plus pegylated Interferon alpha-2b vs ribavirin plus pegylated interferon alpha-2b in therapy nave patients with HCV: phase 3 results. J Hepatol 2006; 44: S273.
17. Hinrichsen H, Benhamou Y, Wedemeyer H, Reiser M, Sentjens RE, Calleja JL, et al. Short term antiviral efficacy of BILN 2061, a hepatitis C virus serine protease inhibitor, in hepatitis C genotype 1 patients. Gastroenterology 2004; 127: 1347-55.
18. Hezode C, Forestier N, Dusheiko G, Ferenci P, Pol S, Goeser T, et al. Telaprevir and peginterferon with or without ribavirin for chronic HCV infection. N Engl J Med 2009; 360: 1839-50.
19. McHutchison JG, Everson GT, Gordon SC, Jacobson IM, Sulkowski M, Kauffman R, et al. Telaprevir with peginterferon and ribavirin for chronic HCV genotype 1 infection. N Engl J Med 2009; 360: 1827-38.
20. Manns MP, Muir A, Adda N, Jacobson I, Afdhal N, Heathcote EJL, et al. Telaprevir in hepatitis C genotype 1 infected patients with prior non-response, viral breakthrough or relapse to peginterferon-alfa-2a/b and ribavirin therapy: SVR results of the PROVE3 study. J Hepatol 2009; 50S: 379.
21. Kwo PY, Lawitz E, McCone J, Schiff E, Vierling J, Pound D, et al. HCV SPRINT-1 final results: SVR 24 from a phase 2 study of boceprevir plus peginterferon alfa-2b/ribavirin in treatment naïve subjects with genotype 1 chronic hepatitis C. J Hepatol 2009; 50S: 4.
22. Lawitz E, Nguyen T, Younes Z, Santoro J, Gitlin N, McEniry D, et al. Clearance of HCV RNA with valopicitabine (NM283) plus peg-interferon in treatment-naive patients with HCV-1 infection: results at 24 and 48 weeks. J Hepatol 2007; 46: 9A.
23. Klumpp K, Leveque V, Le Pogam S, Ma H, Jiang WR, Kang H, et al. The novel nucleoside analog R1479 (4'-azidocytidine) is a potent inhibitor of NS5B-dependent RNA synthesis and hepatitis C virus replication in cell culture. J Biol Chem 2006; 281: 3793-9.
24. Zhou XJ, Pietropaolo K, Sullivan-Bolyai J, Kuca B, Liu W, Xu L, et al. IDX, a liver targeted nucleotide HCV polymerase inhibitor: Results from a first in man safety and pharmacokinetic study. J Hepatol 2009; 50: 351.
25. Villano S, Raible D, Harper D, Speth J, Chandra P, Shaw D, et al. Antiviral activity of the non-nucleoside polymerase inhibitor, HCV-796, in combination with pegylated interferon alfa-2b in treatment naive patients with chronic HCV. J Hepatol 2007; 46: 24A.
26. Jacobson I, Pockros P, Lalezari J, Lawitz E, Rodriguez-Torres M, DeJesus E, et al. Antiviral activity of filibuvir in combination with pegylated interferon alfa-2a and ribavirin for 28 days in treatment naive patients chronically infected with HCV genotype 1. J Hepatol 2009; 50S: 382.
27. Nelson DR, Ghalib RH, Sulkowski M, Schiff E, Rustgi V, Pockros PJ, et al. Efficacy and safety of the cyclophilin inhibitor DEBIO 025 in combination with peginterferon alfa-2a and ribavirin in previously null responder genotype 1 HCV patients. J Hepatol 2009; 50S: 40.
28. Lawitz E, Rouzier R, Nguyen T, Huang D, Ke J, Praestgaard J, et al. Safety and antiviral efficacy of 14 days of the cyclophilin inhibitor NIM811 in combination with peginterferon alfa-2a in relapsed genotype 1 HCV infected patients. J Hepatol 2009; 50S: 379.
29. Hopkins S, Heuman D, Gavis E, Lalezari J, Glutzer E, DiMassimo B, et al. Safety, plasma pharmacokinetics, and anti-viral activity of SCY-635 in adult patients with chronic hepatitis C virus infection. J Hepatol 2009; 50S: 36.
30. Rutter K, Beinhardt S, Kerschner H, Scherzer TM, Hofer H, Popow-Kraupp T, et al. Intravenous silibinin as "rescue treatment" for on treatment nonresponders to full dose of peginterferon/ribavirin combination therapy. J Hepatol 2009; 50S: 235.
31. Bacon B, Shiffman ML. Phase 2 randomized, double-blind, placebo-controlled study of nitazoxanide plus peginterferon and ribavirin in HCV genotype 1 patients: Interim analysis shows increase in EVR. J Hepatol 2009; 50S: 381.
32. Puig M, Major ME, Mihalik K, Feinstone SM. Immunization of chimpanzees with an envelope protein -based vaccine enhances specific humoral and cellular immune response that delay hepatitis C infection. Vaccine 2004; 24: 991-1000.
33. Dagan S, Eren R. Therapeutic antibodies against viral hepatitis. Curr Opin Mol Ther 2003; 5: 148-55.
34. McHutchison J, Bacon B, Gordon SC, Lawitz E, Shiffman ML, Afdhal NH, et al. Final results of a multi-center phase 1b, randomized, placebo-controlled, dose-escalation trial of CPG 10101 in patients with chronic hepatitis c virus. J Hepatol 2006; 44: S49.
35. Shiffman ML, Schiff E, Pockros P, Burgess G, Spanton J, McHutchison J. PF-03491390, (formerly IDN-6556) a pancaspase inhibitor, is well-tolerated and effectively reduces raised aminotransferases (ALT and AST) in chronic active hepatitis C (HCV) patients (pts). Abstract 95. AASLD, Boston, MA, 2006.