Gastroenterology and Hepatology From Bed to Bench

EDITORIAL

HCV infection treatment: a future full of hope

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It is not more than 22 years that non A – non B hepatitis virus was discovered and cloned as a positive stranded enveloped RNA virus belonging to the flavivirus family named Hepatitis C Virus (1).

Shortly after, it was known that like other hepatotropic virus it could have different genotypes with significant nucleotide sequence variability.

HCV infection is a major public health problem infecting as much as 200 million people worldwide and in some parts of the world its prevalence rate reaches up to 30% of the population (2). According to the WHO estimation, without rapid intervention, the mortality due to HCV infection could override the HIV infection. (2) It is the leading cause of chronic hepatitis, cirrhosis, hepatocellular carcinoma (HCC) and a primary indication of liver transplantation in the western world (3).

Following acute HCV infection that often won't be recognised, 15-30% of patients recover spontaneously within the initial 6 months (4). 25% of chronically infected patients will suffer cirrhosis in 30 years with 25% overall chance of its complication such as HCC.

Comprising 6 major genotypes with more than 30% sequence variability and many different subtypes, it exhibits a genetic diversity that seems to be more important than HIV (5). This high genetic variability makes the virus susceptible to select resistant mutation even before drug challenges. Fortunately most of these mutations are non sense and non fit but this could be a limiting factor in direct antiviral agent (DAA) era.

Until recently, the standard of care of HCV therapy was Peg-IFN α (2a or 2b) associated with Ribavirin. This treatment has an overall SVR of 50%.In HCV infection SVR that is defined as persistence of virus negativity 6 months after cessation of treatment, is almost equal to cure. It has been shown that 98% of SVR patients remain virus-free during their whole lifetime. The SVR rate in genotypes 2 and 3 reaches up to 80% in spite of a shorter treatment duration (24 weeks) as compared to genotypes 1 and 4 with an SVR rate of 45% for a duration of 48 weeks (6, 7).

Apart from viral related factors predicting response rate (genotype and viral load) there are many host factors which can determine the response rate (6-9) The host factors could be modifiable such as metabolic co-morbidity, insulin resistance, and alcohol consumption, or non modifiable as the male sex, race and genetic propensity especially SNP on IL28B gene.

It has been shown that the rate of SVR in black patients is lower than in white patients (28% versus 52%) (10). This can be discussed partly by allelic distribution of IL28B gene in different populations.

This IFN λ3 encoding gene is located on chromosome 19 and is highly predictive of success for antiviral treatment.

The chance of SVR in homozygote patients for the C allele at the rs 12979860 or T allele at the rs 8099917 has more than doubled as compared with heterozygote patients or homozygote of non favourable alleles (TT at the rs 12979860 and GG at the 8099917) (11).

It has been demonstrated that the black population has more non favourable allele's distribution contrary to Asiatic population which has more favourable genotypes.

Another biomarker that can predict the response rate is interferon induced protein 10 (IP 10 also referred to as CXCL10) (12). Its high plasma concentration predicts treatment failure. Use of this biomarker with IL 28B could predict the success rate of therapy with higher accuracy.

One of the most important drawbacks of this therapy is its side effects that can lead to premature stop of treatment in a considerable amount of patients. These range from mild musculoskeletal complaint to more advanced end organ damage such as pulmonary, cardiovascular and neuro-psychiatric complications.

Thus there is a great need to develop newer agents having more efficiency and fewer adverse effects as compared with IFN-based regimen.

The HCV enzymes all known as non- structural proteins (NS3/4A, NS4B, NS5A, NS5B) could be a potential target for a direct acting antiviral agent.

After passing different necessary phases of a new drug development, NS3/4A serine protease (α –ketamide linear type), Telaprevir and Boceprevir, have recently been approved in the United States and Europe.

It has been demonstrated that with adding Telaprevir and Boceprevir in back-bone regimen (Peg-IFN and Ribavirin), the SVR rate increases respectively to 73% and 67% in treatment naïve genotype 1 patients (13, 14) and 65% and 66% in treatment experienced patients (15, 16). This obviously shows at least 20% improvement in cure rate. This will be especially interesting when we consider more- difficult- to- treat patients such as cirrhotic ones.

Another positive point of these drugs is their potential chance to impose shorter duration of therapy, ie. 24 weeks instead of 48 weeks. With pursuing the so-called RGT (response guided therapy) in Illuminate study with Telaprevir, 65% of patients were eligible to have 6 months treatment with a SVR rate of 92% (17).

It should be mentioned that these drugs can't be used as monotherapy because of the rapid development of viral resistance (18, 19).

Ribavirin is an essential drug in this regimen. In Prove 2 study, the group taking Ribavirin in addition to Peg-IFN and Telaprevir for 12 weeks had 24% more SVR rate as compared with the group lacking Ribavirin (20). Moreover, Ribavirin reduced the risk of selecting Telaprevir resistance.

This was confirmed recently by an in vitro study which showed the additive antiviral activity of the dual combination of Ribavirin with either of Boceprevir or Telaprevir (21).

Although the exact mechanism of action of Ribavirine to potentiate the IFN antiviral activity remains to be elucidated , it has been shown that it induces the expression of INF stimulated genes namely IRF7 and IR9 (22).

The great drawback of first generation protease inhibitors is their spectrum of activity. These drugs are active against genotype 1 and genotype 2 only. Although our major current problem dealing HCV treatment is genotype 1, which is the most common genotype worldwide and the most resistant to existing antiviral treatment, there is a lot of non genotype 1 HCV-infected patients requiring more active drugs for eradicating virus.

Second generation protease inhibitors such as for instance MK – 5172 have pangenotypic coverage (23). Moreover, new DAA in development including Nucleoside/Nucleotide analogue inhibitors of NS5B (RNA dependent

RNA polymerase) and NS5A inhibitors are active on all known genotypes and subtypes. Several drugs of these classes such as Sofosbuvir (Nucleotide analogue antipolymerase), Mericitabine (Nucleoside analogue antipolymerase) and Daclatasvir (NS5A inhibitor) have reached their late clinical development.

Drugs that are active on host cells could also have pangenotypic coverage. Among them, a cyclophiline inhibitor (Alisporivir), an agent that inhibits HCV replication through mechanisms that remain unclear showed promising antiviral activity (24) but its development was halted by the FDA because of three cases of pancreatitis. Another potential cellular target could be EGFR and EphA2 whose inhibition could reduce viral entry (25).

One of the major determinants of success for the new DAA against HCV and its threat is upcoming resistance mutation. It is known that HCV RNA-dependent RNA polymerase is error-prone so resistance mutation will occur inevitably during direct acting drug usage. It was demonstrated that 5-7% of wild HCV population can have one of their resistance mutations to protease inhibitor, even before any drug challenges, and this rate may go up to 15% for non-nucleoside polymerase inhibitors. This evidence raises concern to verify resistance mutation before any use of DAA. It needs to be addressed by more in depth studies.

Apparently , the resistance mutation will not be archived in HCV genome , although the EXTEND study showed 90% of Telaprevir resistant mutation would disappear within the first two years, but the exact length of their persistence upon drug discontinuation remains to be established. It is noteworthy that the method used in this study was bulk sequencing and not pyrosequencing (ultra sensible method), so the minority variants had chance to be missed.

The advent of new therapy raises the hope reasonably to cure all infected patients and even with implementation of widespread screening to eradicate HCV completely. It is noteworthy, however, that this new regimen will be very expensive and access to it would not be possible for the patients living in low income countries. Keeping in mind that, the majority of HCV-infected patients living in these countries guaranteeing high transmission rate, the difficulty of its total eradication will be more pronounced.

For this reason, with improving the personalized HCV treatment strategy and developing the decision tree serving as road map, we could be able to minimize the use of new drugs with continuing to use dual therapy (Interferon and Ribavirin) in high responsive patients for hoping to reduce the treatment cost.

It could be suggested, with this goal, to do IL28B genotype in less advanced chronic HCV-infected patients (mild to moderate fibrosis) and treat all ideal patients (who have favourable alleles i.e. CC at rs 12979860 or TT at rs 8099917 and who lose HCV on the 4^{th} week of treatment) with Peg-IFN and Ribavirin regimen. The duration of therapy could be reduced to 24 weeks in the patients who have low HCV viral load before therapy (<400000 UI/ml) without any impaction on SVR rate. For all other patients the triple therapy (adding a DAA to backbone regimen) with applying RGT strategy for non cirrhotic and rapid responder patients to reduce the treatment duration to 24 weeks would be a good advisable choice.

In new DAA era, there is some hope to have a treatment regimen without interferon for excluding all its related side effects. The different direct antiviral agents classes (Protease inhibitors, NS5A inhibitors, nucleos(t)ide and non nucleoside RdR polymerase inhibitors) have distinct active sites with own resistant pattern. Thus, there would not be any cross-resistance between these drug classes, while within each

class, the drugs share some resistant mutation. Theoretically, these agents would have some additive and complementary antiviral activities in the way that their combination usage could prevent development of resistance.

INFORM-1 study, for the first time, tested this concept and found some encouraging results (26). Up to 63% of treatment –naïve patients who used, during 2 weeks, a combination of different doses of Mericitabine (antipolymerase) and danoprevir (antiprotease) achieved undetectable HCV RNA level on the second week. They were subsequently treated with Peg-IFN and Ribavirine.

The first successful report of SVR using all oral therapy was with Asunaprevir (protease inhibitor) and Daclatasvir (NS5A inhibitor) that showed 36% SVR rate in prior null responders to Peg-IFN/RBV (27). All patients with breakthrough were infected with genotype 1a whilst all patients who achieved SVR were infected with genotype 1b. This combination has been used also in 10 null responders Japanese patients who were infected with HCV genotype 1b and all of them achieved SVR (28).These studies show low barrier to resistance of Daclatasvir in HCV genotype 1a and would suggest that a DAA combination containing at least one agent with high barrier to resistance could improve SVR rate.

It has been recently presented (EASL, April 2012) that the use of Sofosbuvir (high resistance barrier) in combination with Daclatasvir (relatively low resistance barrier) for 24 weeks achieved 100% SVR4 (29).

We have to wait for the results of clinical trials that are currently evaluating the different DAA combinations for final conclusion and probable establishment all-oral, IFN –free treatment as a first –line regimen for patients with chronic HCV infection.

References

1. Choo QL, Kuo G, Weiner AJ, Overby LR, Bradley DW, Houghton M. Isolation of a cDNA clone derived from a bloodborne non-A, non-B viral hepatitis genome. Science 1989; 244: 359-62.

2. Garrone P, Fluckiger AC, Mangeot PE, Gauthier E, Dupeyrot-Lacas P, Mancip J, et al. A prime-boost strategy using virus-like particles pseudotyped for HCV proteins triggers broadly neutralizing antibodies in macaques. Sci Transl Med 2011; 3: 94ra71.

3. Sharma P, Lok A. Viral hepatitis and liver transplantation. Semin Liver Dis 2006; 26: 285–97.

4. Micallef JM, Kaldor JM, Dore GJ. Spontaneous viral clearance following acute hepatitis C infection: a systematic review of longitudinal studies. J Viral Hepat 2006; 13:34-41.

5. Simmonds P, Bukh J, Combet C, Deléage G, Enomoto N, Feinstone S, et al. Consensus proposals for a unified system of nomenclature of hepatitis C virus genotypes. Hepatology 2005; 42:962–73.

6. 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.

7. Hadziyannis SJ, Sette H Jr, Morgan TR, Balan V, Diago M, Marcellin P, et al. Peginterferon-alpha2a and ribavirin combination therapy in chronic hepatitis C: a randomized study of treatment duration and ribavirin dose. Ann Intern Med 2004; 140:346-55.

8. Foster GR, Fried MW, Hadziyannis SJ, Messinger D, Freivogel K, Weiland O. Prediction of sustained virological response in chronic hepatitis C patients treated with peginterferon alfa-2a (40KD) and ribavirin. Scand J Gastroenterol 2007; 42: 247-55.

9. Ferenci P. Predictors of response to therapy for chronic hepatitis C. Semin Liver Dis 2004; 24:S25-31.

10. Conjeevaram HS, Fried MW, Jeffers LJ, Terrault NA, Wiley-Lucas TE, Afdhal N, et al. Peginterferon and ribavirin treatment in African American and Caucasian American patients with hepatitis C genotype 1. Gastroenterology 2006; 131:470-77.

11. Ge D, Fellay J, Thompson AJ, Simon JS, Shianna KV, Urban TJ, et al. Genetic variation in IL28B predicts hepatitis C treatment-induced viral clearance. Nature 2009; 461:399-401.

12. Albert ML, Casrouge A, Chevaliez S, Hézode C, Rosa I, Renard P, et al. Interferon induced protein 10 remains a useful biomarker of treatment failure in patients stratified for the interleukin-28B rs12979860 haplotype. Hepatology 2011; 53:1410-11.

13. Jacobson IM, McHutchison JG, Dusheiko G, Di Bisceglie AM, Reddy R, Bzowej NH, et al. Telaprevir for previously untreated chronic hepatitis C virus infection. N Engl J Med 2011;365:2405-16.

14. Poordad F, McCone J Jr, Bacon BR, Bruno S, Manns MP, Sulkowski MS, et al. Boceprevir for untreated chronic HCV genotype 1 infection. N Engl J Med 2011; 364:1195-206.

15. Zeuzem S, Andreone P, Pol S, Lawitz E, Diago M, Roberts S, et al. Telaprevir for retreatment of HCV infection. N Engl J Med 2011; 364:2417-28.

16. Bacon BR, Gordon SC, Lawitz E, Marcellin P, Vierling JM, Zeuzem S, et al. Boceprevir for previously treated chronic HCV genotype 1 infection. N Engl J Med 2011; 364:1207-17.

17. Sherman KE, Flamm SL, Afdhal NH. Telaprevir in combination with peginterferon alfa-2a and ribavirin for 24 or 48 weeks in treatment-naı¨ve genotype 1 HCV patients who achieved an extended rapid viral response: final results of phase 3 ILLUMINATE study. Hepatology 2010; 52 (abstract; LB-2).

18. Reesink HW, Zeuzem S, Weegink CJ, Forestier N, van Vliet A, van de Wetering de Rooij J, et al. Rapid decline of viral RNA in hepatitis C patients treated with VX-950: a phase 1b, placebo-controlled, randomized study. Gastroenterology. 2006; 131(4):997-1002.

19. Susser S, Welsch C, Wang Y, Zettler M, Domingues FS, Karey U, et al. Characterization of resistance to the protease inhibitor boceprevir in hepatitis C virus-infected patients. Hepatology 2009; 50:1709-18.

20. 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.

21. Hofmann WP, Chung TL, Osbahr C, Susser S, Karey U, Mihm U, et al. Impact of Ribavirin on HCV replicon RNA decline during treatment with interferon-α and the protease inhibitors boceprevir or telaprevir. Antivir Ther 2011; 16:695-704.

22. Thomas E, Feld JJ, Li Q, Hu Z, Fried MW, Liang TJ. Ribavirin potentiates interferon action by augmenting interferon-stimulated gene induction in hepatitis C virus cell culture models. Hepatology 2011; 53:32-41.

23. Brainard DM, Petry A, van Dyck K, Nachbar RB, De Lepeleire IM, Caro L, et al. Safety and antiviral activity of MK-5172, a novel HCV NS3/4A protease inhibitor with potent activity against known resistance mutants, in genotype 1 and 3 HCV-infected patients. Hepatology 2010; 52:706A-707A.

24. Flisiak R, Feinman SV, Jablowski M, Horban A, Kryczka W, Halota W, et al. The cyclophilin inhibitor Debio 025 combined with PEG IFN alpha 2a significantly reduces viral load in treatment-naïve hepatitis C patients. Hepatology 2009; 49:1460-68.

25. Lupberger J, Zeisel MB, Xiao F, Thumann C, Fofana I, Zona L, et al. EGFR and EphA2 are host factors for hepatitis C virus entry and possible targets for antiviral therapy. Nat Med 2011; 17: 589-95.

26. Gane E, Roberts S, Stedman C, Angus PW, Ritchie B, Elston R, et al. Oral combination therapy with a nucleoside polymerase inhibitor (RG7128) and danoprevir for chronic hepatitis C genotype 1 infection (INFORM-1): a randomised, double-blind, placebocontrolled, dose-escalation trial. Lancet 2010; 376: 1467–75.

27. Lok AS, Gardiner DF, Lawitz E, Martorell C, Everson GT, Ghalib R, et al. Preliminary study of two antiviral agents for hepatitis C genotype1. N Engl J Med 2012; 366:216-24.

28. Chayama K, Takahashi S, Toyota J, Karino Y, Ikeda K, Ishikawa H, et al. Dual therapy with the nonstructural protein 5A inhibitor, daclatasvir , and the nonstructural protein 3 protease inhibitor, asunaprevir, in hepatitis C virus genotype 1b-infected null responders. Hepatology 2012; 55:742-8.

29. Sulkowski M, Rodriguez-torres M, Lawitz E. High sustained virologic response rate in treatment-naïve HCV genotype 1a and 1b patients treated for 12 weeks with an interferon – free all-oral quad regimen:tnterim results. J Hepatol 2012; 56:S560.