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Treatment of chronic hepatitis C virus infection in the near future

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INTRODUCTION

Hepatitis C virus (HCV) is currently the most important cause of cirrhosis and hepatocellular carcinoma in the Western World.[1,2] Remarkably, HCV is probably the only chronic human viral infectious agent that can be completely eradicated. Indeed, the occurrence of a sustained virological response (SVR) is almost always equivalent to a cure of the infection.[3-5] More importantly, SVR is a time tested surrogate marker unequivocally linked to an increase in overall survival rate and lower incidence of hepatic decompensation, hepatocellular carcinoma and need for a liver transplant.[6] For the last ten years HCV treatment has remained virtually unchanged, based almost exclusively on the combination of pegylated interferon alpha (PEG-IFNα) plus ribavirin (RBV).[7-10] On May 2011 a new era started in the treatment of chronic hepatitis C, with the FDA approval of telaprevir (TVR) and boceprevir (BOC). These protease inhibitors were the first direct-acting antivirals (DAAs) to be used in routine clinical practice to treat patients with chronic hepatitis C and are now considered the standard of care for HCV genotype 1.[2] These DAAs increase SVR and are able to shorten therapy in a significant proportion of both treatment-naïve and treatment-experienced chronic HCV infected patients.[11-14] However, the extended adverse event profile and pill burden hamper their widespread clinical use. Two new anti-HCV DAA agents, simeprevir and sofosbuvir, have just submitted their phase 3 data to the FDA and will most likely enter the HCV clinical arena in 2014, with the promise of less side effects, once daily intake and a high probability of shortening therapy.

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MAIN HCV TARGETS FOR DIRECT-ACTING ANTIVIRAL AGENTS

The increased knowledge acquired about the three-dimensional structure and function of most of the HCV proteins, coupled with the development of replicative cell culture systems, has led to the identification of a number of potential targets for direct-acting antiviral (DAA) agents against these viral agent.[15] There are three non-structural (NS) HCV proteins that constitute the main targets of the great majority of the new DAAs in late phase of development:

- NS3/4A protease.
- NS5A replication complex.
- NS5B HCV RNA-dependent RNA polymerase, comprising both nucleoside/nucleotide analogue inhibitors and non-nucleoside inhibitors.

Interestingly, the ending of the denomination of these new agents usually indicates the target of the molecule on the HCV molecule, so that NS3/4A protease inhibitors end in the suffix "previr", NS5A inhibitors end in "asvir" and NS5B polymerase inhibitors end in "buvir".

NEW AGENTS THAT WILL PROBABLY BE AVAILABLE IN 2014

Two new DAAs have already completed the registration trials and filed for "new drug application (NDA)" in the United States FDA: simeprevir, an NS3/4A protease inhibitor filed for NDA in April 2013, while sofosbuvir, an NS5B nucleotide analogue polymerase inhibitor filed the NDA in May 2013. The FDA granted a fast track review status for both drugs, so the result of the hole process could be known as early as December 2013 or until the first quarter of 2014.

SIMEPREVIR (TMC-435)

QUEST-1 and QUEST-2 studies: simeprevir combined with PEG-IFNα plus RBV *vs*. PEG-IFNα plus RBV and placebo for treatment naïve HCV genotype 1 patients

Simeprevir is an investigational HCV NS3/4 protease inhibitor that is active against genotypes 1,2,4,5 and 6.[16] It is taken once daily, at a dose of 150 mg, for 12 weeks in combination with PEG-IFNα plus RBV for 24 to 48 weeks, according to response guided therapy. Two phase three studies conducted in different parts of the world enrolled HCV genotype-1 treatment naïve patients: QUEST-1[17] included 394 patients mainly from United States an Japan, while QUEST-2[18] included 391 patients from around the world, mainly Europe and Latin America. Overall, patients were similar in both trials, with around 10% being cirrhotics, 30% IL28B CC and roughly 50% genotype 1a. Results showed an SVR of 80 and 81% in QUEST-1 and QUEST-2, respectively, *vs*. 50% in controls treated with PEG-IFNα plus RBV in both studies. There was a slightly superior SVR in those treated with Simeprevir plus PEG-IFNα2a compared to PEG-IFNα2b (88% *vs*. 78%, respectively). Around 85-90% of the patients achieved a rapid viral response (RVR), defined as HCV RNA < 25 UI/mL at week 4 and indetectable at week 12 and were able to stop therapy at 24 weeks, with an SVR ranging between 86-91%. Conversely, 10-15% of the patients did not achieve RVR and only 20-30% of these patients achieved an SVR. Patients with cirrhosis had a lower SVR rate in both studies: in QUEST-1, SVR-12 rates in cirrhotics were 58 and 29%, respectively, in the simeprevir and control arms; similarly, in QUEST-2, SVR-12 rates in cirrhotics were 65 and 40%, respectively, in the simeprevir and control arms. It is interesting to note that in QUEST-1, patients with HCV genotype 1a had almost 20% less SVR than HCV genotype 1b, probably associated with mutation Q80K found in approximately 1/3 of genotype 1a patients at baseline. On the contrary, in QUEST-2 this mutation was infrequent and did not impact significantly the SVR rate. Simeprevir was well tolerated, with discontinuation for adverse events below 3% in both studies without significant difference between simeprevir and controls. Simeprevir was associated with pruritus, mild rash (> 99% grade 1 or 2), 4% of photosensitivity, and a transient and mild elevation in indirect bilirrubin levels, without jaundice or elevation in aminotrasnferases.[16-18]

ASPIRE study: simeprevir combined with PEG-IFNα plus RBV *vs*. PEG-IFNα plus RBV and placebo for treatment experienced HCV genotype 1 patients

The ASPIRE[19] trial is a Phase 2b, randomized, double-blind, placebo-controlled study that included 462 treatment-experienced patients with HCV genotype 1 divided according to type of previous response to PEG-IFNα plus RBV treatment: 40% relapsers, 35% partial responders, and 25% null responders. About two-thirds of participants were men, almost all were white, and the median age was 50 years. Around 40% had HCV subtype 1a, most had high HCV viral load at baseline and 17% had IL28B CC. Nearly 20% had Metavir stage F3 and a similar proportion had cirrhosis at baseline. Participants were randomly allocated to receive 100 mg or 150 mg once-daily simeprevir for either 12, 24, or 48 weeks in combination with PEG-IFNα plus RBV for 48 weeks. The control arm received PEG-IFNα plus RBV and placebo. No response guided therapy was used. Among relapsers SVR was 85% with both doses of simeprevir and only 37% in controls; among partial responders SVR was 57% (100 mg simeprevir dose), 75% (150 mg simeprevir dose) and only 9% in controls; among null responders SVR was 46% (100 mg simeprevir dose), 51% (150 mg simeprevir dose) and 19% in controls. Except for relapsers, those with subtype 1b did generally better, as did those with minimal fibrosis compared to F3/F4; among cirrhotic patients, the most difficult group to cure, SVR was only 31%. There was a good overall safety profile. Simeprevir was generally well-tolerated: rates of serious adverse events were 6% in the 100 mg simeprevir arm, 10% in the 150 mg arm, and 6% in the control arm. Rates of discontinuation due to adverse events were 7, 9, and 5%, respectively. Simeprevir recipients were more likely to experience pruritus or skin rash than those in the control arm, but severe rashes were rare (0.5%).

SOFOSBUVIR (GS-7977)

NEUTRINO study: sofosbuvir combined with PEG-IFNα plus RBV for treatment naïve HCV genotype 1,4,5 and 6 patients

Sofosbuvir is a NS5B polymerase inhibitor that is active against all HCV genotypes and has a high barrier to resistance.[20] It is taken once daily, at a dose of 400 mg, for 12 weeks in combination with PEG-IFNα plus RBV. NEUTRINO,[21] a phase 3

open-label, single-arm study, enrolled 327 treatment naïve patients with HCV genotypes 1,4,5 and 6. There was fixed treatment duration of 12 weeks, without use of response guided therapy. Overall, 17% of the patients were cirrhotics and 29% had IL28B CC. Results showed an SVR of 89% for HCV genotype 1 patients and 97% for the 35 patients with genotypes 4,5 and 6. There was no actual control group, however the study used a calculated historical, with an estimated SVR of 60%. Patients with cirrhosis had an SVR of 80%, which was the highest rate reported thus far for a population of patients with cirrhosis in any study. The few failures were relapses. No sofosbuvir resistance was detected, confirming the high genetic barrier of this compound. Grade 3/4 adverse events were reported in 15% of patients, but only 2% discontinued treatment early for adverse events.[16,21] There did not appear to be any additive toxicity of sofosbuvir, although the absence of a real control group impairs the analysis of the side effect profile of sofosbuvir triple therapy compared to dual therapy in this trial.

FISSION, FUSION AND POSITRON studies: sofosbuvir plus RBV for HCV genotype 2 and 3 patients, either treatment-naïve, treatment-experienced, or patients were interferon intolerant, ineligible or unwilling

FISSION,[21] FUSION,[22] and POSITRON[22] tested an all oral combination of sofosbuvir plus RBV for 12 to 16 weeks in almost 1,000 treatment-naïve and treatment-experienced patients with HCV genotypes 2 or 3. Safety was remarkable in all trials and only a minority of the patients discontinued treatment prematurely for adverse events. Results of these three Phase 3 studies are summarized in table 1.

THE FIRST ALL ORAL INTERFERON-FREE COMBINATION OUTSIDE CLINICAL TRIALS: OFF-LABEL USE OF SIMEPREVIR PLUS SOFOSBUVIR?

As soon as simeprevir and sofosbuvir become commercially available, it is possible that some people will entertain the possibility of combining both agents with our without RBV, to create an off-label IFN free regimen. In this regard, it is important to review the results of the COSMOS study.[23] This Phase 2 exploratory trial enrolled two cohorts of HCV genotype 1 null responders: one with fibrosis stage Metavir F0-F2 and the other with F3-F4. Both cohorts were randomized to receive simeprevir plus sofosbuvir with or without RBV for 12 *vs.* 24 weeks of fixed therapy duration. Preliminary results are so far available only for the 12 week arm of the first cohort, with less significant liver fibrosis. Among 27 patients that received simeprevir plus sofosbuvir with RBV, the rate of undetectable HCV RNA 8 weeks after the end of therapy (SVR-8) was 96%. Similarly, among 14 patients treated with simeprevir plus sofosbuvir without RBV, SVR-8 was 93%. Overall, 24 patients already reached 12 weeks of follow-up after the end of therapy and all maintain undetectable HCV RNA (SVR-12). Eight patients reached week 24 follow-up after the end of therapy and also remain HCV RNA undetectable (SVR-24). Only 2% of patients had to interrupt prematurely the trial for adverse events. These results are surely preliminary, however the message they send out is powerful: in some areas of the world we may start to see the first IFN free regimens already being used to treat chronic HCV patients in routine clinical practice as early as 2014.

Table 1. Results of three sofosbuvir Phase 3 studies in HCV genotypes 2 or 3.

Study	Population	Treatment groups	Overall SVR* (n/N)	SVR Gen-2	SVR Gen-3
FISSION	Genotype 2/3 treatment-naïve	Sofosbuvir + RBV for 12 weeks	67% (107/253)	97%	56%
		PEG-IFNα + RBV for 24 weeks	67% (162/243)	78%	63%
POSITRON	Genotype 2/3, IFN intolerant, ineligible or unwilling	Sofosbuvir + RBV for 12 weeks	78% (161/207)	93%	61%
		Placebo for 12 weeks	0% (0/71)	0%	0%
FUSION	Genotype 2/3 treatment-experienced	Sofosbuvir + RBV for 12 weeks	50% (50/100)	86%	30%
		Sofosbuvir + RBV for 16 weeks	73% (69/95)	94%	62%

OTHER DAA AGENTS THAT WILL PROBABLY SOON BE AVAILABLE

Besides simeprevir and sofosbuvir, several other DAA agents are currently in late stages of development. Most will be used without interferon and some even without ribavirin. The majority will not use response guided therapy and will depend on a fixed regimen with a total duration of usually no more than 12 weeks. Side effect profile looks very promising, but the number of patients tested is still small and few cirrhotics have been included. At the moment of this writing, none of these second and third wave agents has yet sent the "new drug application" request to the FDA. Notwithstanding, it is a fact that many of them are also receiving the fast-track analysis status from the FDA and could be commercially available, at least in the United States and parts of Europe, as early as the end of 2014 or early 2015. The main companies and drug combinations that make the bulk of the third wave anti-HCV DAA agents are listed below:

1. BOHERINGER-INGELHEIM.

- The phase 3 trial STARTVerso-1[24] explored the combination of faldaprevir (NS3/4A protease inhibitor) at a dose of 120 mg and 240 mg, taken once daily, plus PEG-IFNα/RBV for 24 to 48 weeks according to response guided criteria *vs.* PEG-IFNa/RBV for 48 weeks in a group of treatment-naïve chronic HCV genotype-1 patients, with an SVR of 79% (faldaprevir 120 mg) *vs.* 80% (faldaprevir 240 mg) *vs.* 52% (PEG-IFNα/RBV), respectively. Importantly, 88% of the patients in the faldaprevir 120 mg arm were able to achieve response guided criteria and shortened therapy to 24 weeks. Safety profile was good However, there were little more than 5% cirrhotics included in this trial.
- Faldaprevir plus deleobuvir (NS5B nonnucleoside polymerase inhibitor) with and without RBV were tested in a randomized, open-label, Phase 2b trial.[25] SVR rates ranged from 56 to 85% among patients with genotype 1b infection *vs.* 11 to 47% among patients with genotype 1a infection and 58 to 84% among patients with IL28B CC *vs.* 33 to 64% with non-CC genotypes. Rash, photosensitivity, nausea, vomiting, and diarrhea were the most common adverse events.

2. ABBVIE.

- The AVIATOR[26] is a Phase 2b study designed to assess the safety and efficacy of ABT-450/r (dosed 100/100 to 200/100 mg once daily), ABT-267 (25 mg once daily), ABT-333 (400 mg twice daily) and ribavirin in non-cirrhotic treatment-naive patients and prior PEG-IFNα/RBV null responders with HCV genotype 1. Duration varied from 8, 12 or 24 weeks of treatment. The 12-week triple-DAA regimen with RBV achieved SVR-12 in 99% of treatment-naive patients and 96% of SVR-24 in intent-to-treat analysis. Furthermore, 93% of prior null responders achieved SVR-12 and SVR-24.

3. GILEAD.

- The ELECTRON[27] study tested Sofosbuvir (NS5B nucleotide polymerase inhibitor) plus ledipasvir (NS5A inhibitor) plus RBV for 12 weeks in a small group of HCV genotype 1 treatment-naive patients (n = 25) and prior null responders (n = 9), without cirrhosis. All patients (100%) achieved SVR-12.

4. BRISTOL-MYERS SQUIBB.

- The COMMAND-1[28] was a randomized, double-blinded, placebo-controlled, Phase 2b clinical study of daclatasvir (NS5A inhibitor) plus PEG-IFNα/RBV for 24 to 48 weeks in treatment-naïve chronic HCV genotype-1 (n = 365) or 4 (n = 30) infected patients. Each treatment group included 5-10% compensated cirrhotic patients. The SVR-12 was 65% for genotype 1 and reached 100% in one of the genotype 4 arms. SVR was better among geno-type 1b compared to 1a (87% *vs.* 58%, respectively). Tolerability was good overall.
- The COMMAND-2[29] study explored the combination of daclatasvir (NS5A inhibitor) plus PEG-IFNα/RBV for 12 to 16 weeks *vs.* PEG-IFNα/RBV for 24 weeks in 151 treatment-naïve chronic HCV genotype-2 or 3 patients. SVR-12 among genotype-2 patients was 88%, 83% and 63% in the daclatasvir 12 weeks, 16 weeks and controls, respectively. SVR-12 among genotype-3 patients was 69, 70 and 59% in the daclatasvir 12 weeks, 16 weeks and controls, respectively. Side-effects were those commonly experienced with PEG-IFNα/RBV alone.

- The combination of daclatasvir (NS5A inhibitor) plus asunaprevir (NS3/4A protease inhibitor) plus BMS-791325 (non-nucleoside NS5B inhibitor) was studied in a randomized, open-label, Phase 2 trial in treatment-naïve patients with HCV Genotype 1 infection and without cirrhosis.[30] Of the 66 enrolled patients, 74% had genotype 1a infection and 30% had IL-28B CC genotype. The SVR-12 rate ranged from 88 to 94%, with no significant difference between 12 and 24 weeks. Tolerability was good overall.

5. BRISTOL-MYERS SQUIBB PLUS GILEAD.

- Daclatasvir (NS5A inhibitor) plus sofosbuvir (NS5B nucleotide polymerase inhibitor) for 12 to 24 weeks has 100% rate of SVR in treatment-naïve chronic HCV genotype-1, 2 and 3 patients.[31]
  In another study,[32] a total of 41 HCV genotype 1 patients with previous failure to telaprevir and boceprevir were randomly assigned to daclatasvir 60 mg once daily plus sofosbuvir 400 mg once daily with or without ribavirin for a total of 24 weeks. Patients with cirrhosis were excluded. The majority had HCV genotype 1a and 98% of patients had a non-CC IL-28B genotype. SVR-12 was 100%.

CONCLUSION

Treatment of chronic HCV infection has a remarkable history of success almost without parallel in the field of medicine. Besides HCV, there is probably no other chronic human viral infection that can be totally eradicated with antiviral treatment. Currently, the standard of care for HCV genotype 1 patients is the use of TVR or BOC combined with PEG-IFNα plus RBV. Two new anti-HCV DAA agents, simeprevir and sofosbuvir, with a better safety profile and comparable, if not higher, efficacy are expected to be approved soon by the United States FDA. It is reasonable to assume that both drugs will be available in North America and some European countries already at the end of 2013 or early 2014. Time will tell if these first second wave DAA agents will prove to be safe and effective when used in large numbers of real life chronic HCV infected patients. It is conceivable that off-label use of these agents could start to pave the way for the third wave of all oral IFN-free treatment of chronic hepatitis C: The game's afoot.[33]

REFERENCES

1. EASL Clinical Practice Guidelines. Management of hepatitis C virus infection. *J Hepatology* 2011; 55: 245-64.
2. Ghany MG, Nelson DR, Strader DB, et al. An Update on Treatment of Genotype 1 Chronic Hepatitis C Virus Infection: 2011 Practice Guideline by the American Association for the Study of Liver Diseases. *Hepatology* 2011; 54: 1433-44.
3. Manns MP, Pockros PJ, Norkrans G, et al. Long-term clearance of hepatitis C virus following interferon α-2b or peginterferon α-2b, alone or in combination with ribavirin. *J Viral Hepat* 2013; 20: 524-9.
4. Bruno S, Crosignani A, Facciotto C, et al. Sustained virologic response prevents the development of esophageal varices in compensated, Child-Pugh class A hepatitis C virus-induced cirrhosis. A 12-year prospective follow-up study. *Hepatology* 2010; 51: 2069-76.
5. Morgan TR, Ghany MG, Kim HY, et al. Outcome of sustained virological responders with histologically advanced chronic hepatitis C. *Hepatology* 2010; 52: 833-44.
6. van der Meer AJ, Veldt BJ, Feld JJ, et al. Association between sustained virological response and all-cause mortality among patients with chronic hepatitis C and advanced hepatic fibrosis. *JAMA* 2012; 308: 2584-93.
7. Zeuzem S, Andreone P, Pol S, et al. Telaprevir for retreatment of HCV infection. *N Engl J Med* 2011; 364: 2417-28.
8. Manns MP, McHutchison JG, Gordon SC, et al. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial. *Lancet* 2001; 358: 958-65.
9. Fried MW, Shiffman ML, Reddy KR, et al. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. *N Engl J Med* 2002; 347: 975-82.
10. Hadziyannis SJ, Sette H Jr., Morgan TR, 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.
11. Poordad F, McCone J Jr, Bacon BR, et al. Boceprevir for untreated chronic HCV genotype 1 infection. *N Engl J Med* 2011; 364: 1195-206.
12. Bacon BR, Gordon SC, Lawitz E, et al. Boceprevir for previously treated chronic HCV genotype 1 infection. *N Engl J Med* 2011; 364: 1207-17.
13. Jacobson IM, McHutchison JG, Dusheiko G, et al. Telaprevir for previously untreated chronic hepatitis C virus infection. *N Engl J Med* 2011; 364: 2405-16.
14. Zeuzem S, Andreone P, Pol S, et al. Telaprevir for retreatment of HCV infection. *N Engl J Med* 2011; 364: 2417-28.
15. Sarrazin C, Hézode C, Zeuzem S, Pawlotsky JM. Antiviral strategies in hepatitis C virus infection. *J Hepatol* 2012; 56(Suppl. 1): S88-S100.
16. A SPECIAL MEETING REVIEW EDITION: Advances in the Treatment of Hepatitis C Virus Infection From EASL 2013: The 48th Annual Meeting of the European Association for the Study of the LiverApril 24-28, 2013 • Amsterdam, The NetherlandsSpecial Reporting on:• Simeprevir Plus Peginterferon/Ribavirin Is Associated with a High SVR12 Rate in Treatment-Naive Patients with Genotype 1 Hepatitis C Virus Infection• Addition of Simeprevir to Peginterferon/Ribavirin Is Associated with Faster Resolution of Fatigue in Treatment-Naive Patients• Sofosbuvir Plus Ribavirin Demonstrates Significant Efficacy in Multiple HCV Genotype 2/3 Populations• Daclatasvir Plus Sofosbuvir with or without Ribavirin Yields 100% SVR24 Rate in Genotype 1 Patients Who Fail Telaprevir or Boceprevir• Addition of

TG4040 Vaccine to Peginterferon/Ribavirin Increases Sustained Virologic Response Rate at 24 Weeks in Genotype 1 Hepatitis C InfectionPLUS Meeting Abstract Summaries With Expert Commentary by: Ira M. Jacobson, MDJoan Sanford I. Weill Medical College at Cornell UniversityNew York, New York. *Gastroenterol Hepatol (NY)* 2013; 9(Suppl. 3): 1-18.

17. Jacobson I, Dore GJ, Foster GR, et al. Simeprevir (TMC435) with peginterferon/ribavirin for chronic HCV genotype 1 infection in treatment-naïve patients: results from QUEST-1, a phase III trial. Presented at the 48th Annual Meeting of the European Association for the Study of the Liver; April 24–28, 2013; Amsterdam, the Netherlands. Abstract 1525.
18. Manns M, Marcellin P, Poordad FP, et al. Simeprevir (TMC435) with peginterferon/ribavirin for treatment of chronic HCV genotype-1 infection in treatment- naive patients: results from QUEST-2, a phase III trial. Presented at the 48th Annual Meeting of the European Association for the Study of the Liver; April 24–28, 2013; Amsterdam, the Netherlands. Abstract 1413.
19. Zeuzem S, Berg T, Gane E, et al. TMC435 in HCV genotype 1 patients who have failed previous pegylated interferon/ ribavirin treatment: final SVR24 results of the ASPIRE trial. Presented at the 47th Annual Meeting of the European Association for the Study of the Liver; April 18–22, 2012; Barcelona, Spain. Abstract 2.
20. Gane EJ, Stedman CA, Hyland RH, et al. Nucleotide polymerase inhibitor sofosbuvir plus ribavirin for hepatitis C. *N Engl J Med* 2013; 368: 34-44.
21. Lawitz E, Mangia A, Wyles D, et al. Sofosbuvir for previously untreated chronic hepatitis C infection. *N Engl J Med* 2013; 368: 1878-87.
22. Jacobson IM, Gordon SC, Kowdley KV, et al. Sofosbuvir for hepatitis C genotype 2 or 3 in patients without treatment options. *N Engl J Med* 2013; 368: 1867-77.
23. Lawitz E, Ghalib R, Rodriguez-Torres M, et al. Suppression of Viral Load through 4 Weeks Post-Treatment Results of a Once-daily Regimen of Simeprevir + Sofosbuvir with or without Ribavirin in Hepatitis C Virus GT 1 Null Responders. 20th Conference on Retroviruses and Opportunistic Infections. Atlanta, March 3-6, 2013. Abstract 155LB.
24. Ferenci P, Asselah T, Foster GR, et al. Falaprevir plus pegylated interferon alfa2a and ribavirin in chronic HCV genotype-1 treatment-naïve patients: Final results from STARTVERSO1, a randomized, placebo-controlled phase III trial. 48th Annual Meeting of the European Association for the Study of the Liver, April 24-28, 2013, Amsterdam, Netherlands; abstract 1416.
25. Zeuzem S, Soriano V, Asselah T, et al. Faldaprevir and deleobuvir for HCV genotype 1 infection. *N Engl J Med* 2013; 369: 630-9.
26. Kowdley KV, Lawitz E, Poordad F, et al. A 12-week interferon-free treatment regimen with ABT-450/r, ABT-267, ABT-333 and ribavirin achieves SVR rates (observed data) of 99% in treatment-naïve patients and 93% in prior null responders with HCV genotype 1 infection. 63rd Annual Meeting of the American Association for the Study of Liver Diseases (AASLD 2012). Boston, November 9-13, 2012. Abstract LB-1.
27. Gane E, Stedman CA, Hyland RH, et al. All-oral sofosbuvir-based 12-week regimens for the treatment of chronic HCV infection: the ELECTRON study. 48th Annual Meeting of the European Association for the Study of the Liver (EASL 2013). Amsterdam. April 24-28, 2013. Abstract 14.
28. Hezode C, Hirschfield G, Ghesquiere W, et al. Daclatasvir, an NS5A Replication Complex Inhibitor, Combined With Peginterferon Alfa-2a and Ribavirin in Treatment-Naive HCV-Genotype 1 or 4 Patients: Phase 2b COMMAND-1 SVR12 Results. *Hepatology* 2012; 56(Suppl. 1): 553A. Abstract 755.
29. Dore GJ, Lawitz E, Hezode C, et al. Daclatasvir combined with peginterferon alfa 2a alfa-and ribavirin for 12 or 16 weeks in patients with hepatitis c virus genotype 2 or 3 infection: command gt 2/3 study. Presented at the 48th Annual Meeting of the European Association for the Study of the Liver; April 24–28, 2013; Amsterdam, the Netherlands. Abstract 1418.
30. Everson GT, Sims KD, Rodriguez-Torres M, et al. Interim analysis of an interferon (IFN)- and ribavirin (RBV)-free regimen of daclatasvir (DCV), asunaprevir (ASV), and BMS-791325 in treatment-naive, hepatitis C virus genotype 1-infected patients. Presented at the 48th Annual Meeting of the European Association for the Study of the Liver; April 24–28, 2013; Amsterdam, the Netherlands. Abstract 1417.
31. Sulkowski MS, Gardiner DF, Rodriguez-Torres M, et al. High rate of sustained virologic response with the all-oral combination of daclatasvir (NS5A inhibitor) plus sofosbuvir (nucleotide NS5B inhibitor), with or without ribavirin, in treatment-naïve patients chronically infected with HCG GT 1, 2, or 3. Presented at the 63rd Annual Meeting of the American Association for the Study of Liver Diseases; November 9–13, 2012; Boston, Massachusetts. Abstract LB-2.
32. Sulkowski MS, Gardiner DF, Rodriguez-Torres M, et al. Sustained virologic response with daclatasvir plus sofosbuvir plus/minus ribavirin (RBV) in chronic HCV genotype (GT) 1-infected patients who previously failed telaprevir (TVR) or boceprevir (BOC). Presented at the 48th Annual Meeting of the European Association for the Study of the Liver; April 24–28, 2013; Amsterdam, the Netherlands. Abstract 1417.
33. Shakespeare W. Henry V (act 3, scene 1).