Journal of Infectious Diseases and Therapy
ISSN: 2332-0877

Ferenci, J Infect Dis Ther 2014, 2:2
DOI: 10.4172/2332-0877.1000130

Review Article Open Access

Breakthroughs in Treatment of Chronic Hepatitis C - Time for an Obituary for Peginterferon/Ribavirin?

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Abstract

Within 2 years after licensing peginterferon/ribavirin and first generation protease inhibitors (telaprevir, boceprevir) for treatment of chronic hepatitis C the speed of development of new treatments has substantially increased. Combinations of various direct acting antivirals (DAA) like protease inhibitors (simeprevir, faldaprevir, ABT-450), HCV NS5A inhibitors (ie. daclatasvir, ledipasvir, ABT-267) and HCV RNA polymerase inhibitors (sofosbuvir, ABT-333) are highly effective and can cure hepatitis C without major side effects within 12 weeks. Once these combinations are approved by FDA and EMA they are likely to provide an interferon/ribavirin free treatment.

Introduction

Infection with the Hepatitis C virus (HCV) leads to chronic liver disease and a substantial proportion of patients develop late complications like cirrhosis and hepatocellular carcinoma. In Europe and North America HCV infection is the leading cause for liver transplantation. Therefore effective and safe treatments are an urgent medical need.

The first treatment approach was interferon monotherapy, even before the virus was discovered [1]. This treatment was not very effective and was associated with substantial side effects. Several approaches improved the overall efficacy, like the addition of ribavirin, the development of pegylated interferons and of direct acting antivirals (DAA). A major breakthrough was the licensing of DAA containing triple therapies in 2011 [2,3]. While the efficacy of treatment gradually increased, safety issues became a limiting factor for the use of this therapy [4]. From this moment on the speed of development of new treatments has substantially increased. Like the dual combination the triple combinations with first generation DDA's are associated with unpleasant, sometimes lethal adverse effects.

Therefore treatment regimes not needing a peginterferon/ribavirin backbone are a major unmet medical need. The first proof of concept study of an interferon free therapy was presented in 2010 [5].

Today we have 3 different categories of DAA's which inhibit viral replication at different sites and can be combined for treatment of hepatitis C:

Protease inhibitors prevent viral replication by interacting with the NS3/4 protease

This enzyme is required to split the HCV polyprotein in its active components. Today 3 protease inhibitors are available: telaprevir (Incivo®, Incivec®), boceprevir (Victrelis®) and Simeprevir (Sovriad®, Olysio®), and several more are in clinical development. Because of their low genetic barrier protease inhibitors require a peginterferon/ribavirin backbone.

NS5A-inhibitors

The function of the NS5A protein is not fully known. Its role appears to be to move messenger RNA to the replication complex. No licensed NS5A inhibitor is available today, but partly yet unpublished data indicate that NS5A inhibitors are highly effective in combination with other DAA's. The best investigated ones are daclatasvir, ledipasvir and ABT 267.

Polymerase inhibitors

They act via the replication complex. There are direct (nuc polymerase inhibitors) and indirect inhibitors (non nuc-polymerase inhibitors). Nuc polymerase inhibitors are chain terminators, while non nuc polymerase inhibitors allosterically modify the polymerase. Sofar, only one nuc-polymerase inhibitor is licensed in Europe, USA, and Canada: Sofosbuvir (Sovaldi®).

This nuc-polymerase inhibitor is the most effective currently available DAA. For HCV genotypes 1,4-6 it was tested combined with peginterferon/ribavirin given for 12 weeks and achieved a sustained virologic response (SVR) rate of > 90% [6]. The safety profile was comparable to that of peginterferon/ribavirin dual therapy.

Based on these data Sofosbuvir was approved both by FDA and EMA. Clearly, this new treatment is far from perfect. For genotype 1, the most common genotype in Europe, Japan and North America, it still requires peginterferon and ribavirin, which is poorly tolerated by patients with advanced liver disease.

Interferon Free Combinations

Sofosbuvir + Ribavirin

In patients with genotypes 2 and 3 sofosbuvir was tested as interferon free regime in combination with ribavirin (Table 1). After 12 weeks treatment SVR rates of 86-100% were obtained in non-cirrhotic genotype 2 patients. The results for genotype 3 were less convincing, in patients treated for 12 to 16 weeks response rates were similar than in patients treated with peginterferon/ribavirin [7,8]. Only non-cirrhotic patients treated for 24 weeks had substantially higher SVR rates [9]. Treatment-related health related quality of life (HRQL) impairment during SOF and RBV regimen is mild, and does not increase with longer treatment duration. No new side effects were observed. Achieving SVR-12 with SOF and ribavirin is associated with an improvement in HRQL [10].

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Received January 28, 2014; **Accepted** February 21, 2014; **Published** February 25, 2014

Citation: Ferenci P (2014) Breakthroughs in Treatment of Chronic Hepatitis C - Time for an Obituary for Peginterferon/Ribavirin? J Infect Dis Ther 2: 130. doi:10.4172/2332-0877.1000130

Study	SVR12 (%)	
	GT2	GT3
FISSION (1)		
SOF/RBV 12 Weeks	68/70 (97,1%)	102/183 (55,7)
Peg-IFN/RBV 24 Weeks	52/67 (77,6%)	110/176 (62,5)
POSITRON (2)		
SOF/RBV 12 Weeks		
All	101/109 (93)	60/98 (61)
No Cirrhosis	85/92 (92)	57/84 (68)
Cirrhosis	16/17 (94)	3/14 (21)
FUSION (2)		
SOF/RBV 12 Weeks		
All	31/36 (86,1)	19/64 (29,7)
No Cirrhosis	25/26 (96,2)	14/38 (36,8)
Cirrhosis	6/10 (60)	5/26 (19,2)
SOF/RBV 16 Weeks		
All	30/32 (93,8)	39/63 (61,9)
No Cirrhosis	23/23 (100)	25/40 (62,5)
Cirrhosis	7/9 (77,8)	14/23 (60,9)
VALENCE (9)		
SOF/RBV GT2: 12 Weeks; GT3: 24 Weeks		
Alle	68/73 (93)	212/250 (85)
treatment-naive, all	31/32 (97)	98/105 (93)
no Cirrhosis Cirrhosis	29/30 (97) 2/2 (100)	86/92 (94) 12/13 (92)
Treatment experienced, all	37/41 (90)	112/145 (77)
no Cirrhosis Cirrhosis	30/33 (91) 7/8 (88)	87/100 (87) 27/45 (60)

GT = Genotype; RBV = Ribavirin; SOF = Sofosbuvir; SVR12 = sustained virologic response after 12 Weeks follow up

Table 1: Interferon free studies with Sofosbuvir (SOF) with ribavirin (RBV).

	+RBV	-RBV	+RBV	-RBV
	12 weeks		24 weeks	
Tx naive				
F0-2				
F3-4	100	100		
Tx-experienced				
F0-2	96	92.9	79.2	93.3
F3-4	100	93.3		

Table 2: Interim analysis of the COSMOS study (SVR 12 in patients who completed treatment and follow up).

Patients with the highest need for an effective antiviral regime are patients awaiting liver transplantation. Treatment with Sofosbuvir / ribavirin was started while the patient was on the waiting list and was continued until transplantation. Except for one, all patients treated sufficiently long (≥30 days) to achieve undetectable HCV-RNA before transplantation, experienced no reinfection of the graft [11].

Interferon and Ribavirin Free Combinations

Simeprevir (SMV) + Sofosbuvir

The COSMOS study was a Phase II, randomized, open-label study investigating efficacy/safety of SMV+SOF ± ribavirin (RBV) for 12/24 weeks in HCV genotype 1(GT1) patients (pts) with METAVIR score F0-F2 who were prior null responders to Peg IFN/RBV (cohort 1, n=80) or treatment-naïve patients and prior null responders with F3-F4 (cohort 2). Patients were randomized to SMV (150mg QD) +SOF (400mg QD) ± RBV for 12 weeks, or SMV+SOF ± RBV for 24weeks.

Cohort 2 (n=84) consisted of treatment-naïve and null responders with METAVIR F3-4 the majority (78%) of patients had genotype 1a, 40% had detectable Q80K mutation at baseline (a common preexisting mutation in North American GT1a patients, associated with impaired response to Simeprevir), 47% were cirrhotic and 54% had a previous null response to dual therapy. Even in this more difficult to treat patient population including a fair amount of cirrhotic null-responders overall SVR4 rates were very high suggesting great efficacy of this combination (Table 2). The addition of ribavirin did not add much in terms of cure rates, highlighting that DAA combinations may emerge were ribavirin can be left out. This would be highly attractive with regard to its safety profile plus inability to use it in renal insufficiency. Obviously this prompts the question whether this may be a good combination for more difficult to treat patient populations who are unable to take an interferon-containing HCV regimen.

Daclatasvir (DCV) +Sofosbuvir

In an open-label study [12] 44 previously untreated genotype 1patients with HCV infection and 44 genotype 2 or 3 patients received 60 mg daclatasvir QD plus 400 mg sofosbuvir QD for 24 weeks. The study was expanded to 123 additional patients with genotype 1 infection treated with daclatasvir plus sofosbuvir, with or without ribavirin, for 12 weeks (82 previously untreated patients) or 24 weeks (41 patients who had previous virologic failure with telaprevir or boceprevir plus peginterferon alfa-ribavirin). Patient were randomized to be treated with or without ribavirin.

Among patients with genotype 1 infection, 98% of 126 previously untreated patients and 98% of 41 patients who did not have a sustained virologic response with HCV protease inhibitors had a sustained virologic response at week 12 after the end of therapy. A total of 92% of 26 patients with genotype 2 infection and 89% of 18 patients with genotype 3 infection had a sustained virologic response at week 12. High rates of sustained virologic response at week 12 were observed among patients with HCV subtypes 1a and 1b (98% and 100%, respectively) and those with CC and non-CC IL28B genotypes (93% and 98%, respectively), as well as among patients who received ribavirin and those who did not (94% and 98%, respectively).

Ledipasvir +Sofosbuvir

Ledipasvir is an investigational NS5A inhibitor from GILEAD. The data of the 3 phase III studies of the combination of Sofobuvir and Ledipasvir were communicated by a press release on December 18, 2013. These data have not been peer reviewed, may be incomplete, and we await presentation or publication in a peer-reviewed format. The data are summarized in Table 3.

Study	Patients	N		Duration	SVR 12
ION 1	GT1, naive	865	SOF/LDV	12	97.7%
	15% cirrhosis		SOF/LDV/RBV	12	97.2%
			SOF/LDV	24	NA
			SOF/LDV/RBV	24	NA
ION 2	GT1, Tx exp.	440	SOF/LDV	12	93.6%
	20% cirrhosis		SOF/LDV/RBV	12	96.4%
			SOF/LDV	24	99.1%
			SOF/LDV/RBV	24	99.1%
ION 3	GT1, naive	647	SOF/LDV	8	94.0%
			SOF/LDV/RBV	8	93.1%
			SOF/LDV	12	95.4%

NA= not available

Table 3: Phase 3 Studies of the combination Sofosbuvir (SOF) with Ledipasvir (LDV).

	GT	patients	N	Treatment	SVR (%)
Sapphire I*	1	Tx naive	631	3D+RBV 12 wks	96
Sapphire II*	1	Tx experienced	491	3D+RBV 12 wks	96
Pearl II	1b	Tx experienced	179	3D+RBV 12 wks 3D 12 wks	97 100
Pearl III	1b	Tx naive	419	3D+RBV 12 wks 3D 12 wks	99 99.5
Pearl IV	1a	Tx naive	305	3D+RBV 12 wks 3D 12 wks	97 90
Turquoise II	1	Cirrhotics: Tx naïve +experienced	394	3D+RBV 12 wks 3D+RBV 24 wks	92 96

Table 4: Phase 3 studies with rABT-450+ABT-267+ABT-333 (3D).

Data were reported in a press release from AbbVie (Jan 31, 2014)
* Placebo controlled

Asunaprevir +Daclatasvir

A proof-of-concept study of the combination of the NS5A inhibitor daclatasvir and the protease inhibitor asunaprevir showed that a sustained virologic response can be achieved without peginterferon and ribavirin therapy [13]. The first phase III trial evaluated the safety and efficacy of a PEG/RBV-free, dual oral therapy with daclatasvir 60 mg once daily and asunaprevir 100 mg twice daily for 24 weeks. Interferon ineligible/intolerant naive (n=135) and non-responder (n=87) Japanese patients infected with HCV genotype 1b [14]. As in Japan the HCV GT1b is by far the most common genotype found and as 1b is in general easier to treat, different treatment regimens may work in this particular population as in a more typical North American patient population with mostly GT1a and a less favorable IL28b genotype distribution than in Japan. The median age of patients was 62.5 years, 65% were female, and 10% were cirrhotic, mean baseline HCV RNA was 6.6 log10IU/mL. Naive patients were primarily CC IL28B genotype (70%), 82% of NR patients were non-CC IL28B genotype (rs12979860). A SVR 24 was reached in 87.4 % and 80.5 % of interferon ineligible/intolerant naïve and non responders, respectively. The most common AEs were nasopharyngitis (30%) increased ALT (16%) and AST (13%), headache (15%), diarrhea (10%), and pyrexia (10%). Most discontinuations were due to ALT/AST elevations. Clearly hepatoxicity potential of this combination warrants close monitoring and larger studies will be needed. In contrast to the favorable response rates of GT1b patients the results in GT1a patients were disappointing [13].

Other interferon/ribavirin free regimes

Several combinations of other DAA's are currently in phase 2. The most advanced one is the combination of MK-5172 (a potent second generation HCV NS3/4A protease inhibitor) and MK-8742 (a potent HCV NS5A replication complex inhibitor [15] given for 12 weeks. The available results are encouraging with SVR rates >90%.

Interferon And Ribavirin Free Combination Of 3 DAA

Daclatasvir / asunaprevir with BMS-791325

To optimize treatment results daclatasvir with asunaprevir were combined with the non-nucleoside NS5B inhibitor BMS-791325. By this combination a SVR was achieved in >90% in pilot cohorts of non-cirrhotic patients with HCV genotype 1 infection. This 3 DAA regimen was presented in larger cohorts that included cirrhotic patients [16]. 166 treatment-naïve, HCV GT1-infected patients were randomly assigned (1:1) to receive a twice-daily regimen of DCV 30mg, ASV 200mg, and "325" 75mg (n=80) or 150mg (n=86) for 12 weeks. Randomization was stratified by GT1 subtype and presence of cirrhosis. The all oral 3 DAA regimen with DCV/ASV/BMS-791325 achieved SVR12 in >90% of patients despite prevalence of GT1a or advanced fibrosis/cirrhosis. The therapy was overall well tolerated with low rates of adverse events and treatment discontinuations.

ABT-450 + ABT-267+ ABT-333

In a phase 2 study an interferon-free combination of the protease inhibitor ABT-450 with ritonavir (ABT-450/r) with ribavirin, with or without the NS5A inhibitor ABT-267 or the non nucleoside polymerase inhibitor ABT-333 or both was investigated in patients with HCV genotype 1 infection. 571 patients without cirrhosis who had not received treatment previously or who had not had a response to prior therapy were randomly assigned to treatment for 8, 12, or 24 weeks [17]. Among the 161 previously untreated patients who received treatment three direct-acting antiviral agents plus ribavirin the rate of SVR at 24 weeks after treatment were 88% among those who received the therapy for 8 weeks and 95% among those who received the therapy for 8 and 12 weeks, respectively. In the meantime, six phase three studies with the triple DAA combination were performed. The data on these studies were communicated by press releases on December 10, 2013 and January 31, 2014 (see Table 4). Again, these data have not been peer reviewed, may be incomplete, and we await presentation or publication in a peer-reviewed format.

In summary, these encouraging results indicate, that peginterferon/ribavirin will not be needed in the future for treatment of chronic hepatitis C. Approval of some of these new DAA combinations is expected for the first quarter of 2015. Thus, treatment of hepatitis C will become short, safe and simple to administer. The highest benefit will be experienced in patients with the highest need for treatment who do not tolerate interferon (like patients with decompensated cirrhosis, pre- and post transplant patients) at all. The real challenge will be to make these drugs available to all patients, not just to those who can afford to buy them [18].

Financial Disclosures

Peter Ferenci is a member of the global advisory board and of the speaker's bureau of ROCHE, Basel CH and Rottapharm-Madaus, Monza, Italy. He is also advisor to Böhringer-Ingelheim, Vertex/Tibotec, Idenix, Achilleon, Glaxo Smith-Kline, Gilead and MSD and receives an unrestricted research grant from ROCHE Austria and MSD Austria.

References

1. Hoofnagle JH, Mullen KD, Jones DB, Rustgi V, Di Bisceglie AM et al. (1986) Treatment of Chronic Non-A, Non-B Hepatitis with Recombinant Human Alpha Interferon. N Engl J Med 315:1575-157
2. Jacobson IM, McHutchison JG, Dusheiko G, Di Bisceglie AM, Reddy KR, et al. (2011) Telaprevir for previously untreated chronic hepatitis C virus infection. N Engl J Med 364: 2405-2416.
3. Poordad F, McCone J Jr, Bacon BR, Bruno S, Manns MP, et al. (2011) Boceprevir for untreated chronic HCV genotype 1 infection. N Engl J Med 364: 1195-1206.
4. Ferenci P, Dusheiko G (2013) Beyond phase 3 registration trials: defining safety for triple therapy with protease inhibitors in cirrhosis. Gut .
5. Gane E, Roberts S, Stedman C, Angus P, Ritchie B, Elston R et al. (2010) Oral combination therapy with a nucleoside polymerase inhibitor (RG7128) and danoprevir for chronic hepatitis C genotype 1 infection (INFORM-1): a randomised, double-blind, placebo-controlled, dose-escalation trial. The Lancet 376:1467–1475
6. Lawitz E, Mangia A, Wyles D, Rodriguez-Torres M, Hassanein T, et al. (2013) Sofosbuvir for previously untreated chronic hepatitis C infection. N Engl J Med 368: 1878-1887.
7. Jacobson IM, Gordon SC, Kowdley KV, Yoshida EM, Rodriguez-Torres M, et al. (2013) Sofosbuvir for hepatitis C genotype 2 or 3 in patients without treatment options. N Engl J Med 368: 1867-1877.

8. Gane EJ, Stedman CA, Hyland RH, Ding X, Svarovskaia E, et al. (2013) Nucleotide polymerase inhibitor sofosbuvir plus ribavirin for hepatitis C. N Engl J Med 368: 34-44.

9. Zeuzem S, Dusheiko GM, Salupere R, Mangia A, Flisiak R, Hyland RH et al. Sofosbuvir + Ribavirin for 12 or 24 Weeks for Patients with HCV Genotype 2 or 3: the VALENCE trial. Hepatology 2013;58 (Suppl):733A

10. Younossi ZM, Stepanova M2, Henry L3, Gane E4, Jacobson IM5, et al. (2013) Minimal impact of sofosbuvir and ribavirin on health related quality of life in Chronic Hepatitis C (CH-C). J Hepatol .

11. Curry MP, Forns X, Chung RT. Terrault N, Brown RS, et al. (2013) PretransplantSofosbuvir and Ribavirin to Prevent Recurrence of HCV Infection after Liver Transplantation. Hepatology58:314A

12. Sulkowski MS, Gardiner DF, Rodriguez-Torres M, Reddy KR, Hassanein T, et al. (2014) Daclatasvir plus sofosbuvir for previously treated or untreated chronic HCV infection. N Engl J Med 370: 211-221.

13. Lok AS, Gardiner DF, Lawitz E, Martorell C, Everson GT, et al. (2012) Preliminary study of two antiviral agents for hepatitis C genotype 1. N Engl J Med 366: 216-224.

14. Chayama K, Suzuki Y, Ikeda K, Toyota J, Karino Y, et al.(2013) All-oral Combination of DaclatasvirPlusAsunaprevir in Interferon Ineligible Naive/ Intolerant and Nonresponder Japanese Patients Chronically Infected with HCV Genotype 1b: Results from a Phase 3 Trial. Hepatology58: 313A

15. Lawitz E, Vierling JM, Murillo A, Kugelmas M, GerstoftJ et al.(2013) High Efficacy and Safety of the All-Oral Combination Regimen, MK-5172/MK-8742 +/- RBV for 12 Weeks in HCV Genotype 1 Infected Patients: The C-WORTHY Study. Hepatology 58:244

16. Everson GT, Sims KD, Thuluvath PJ, Lawitz E, Hassanein T, et al. (2013) Phase 2b study of the interferon-free and ribavirin-free combination of daclatasvir, asunaprevir, and BMS-791325 for 12 weeks in treatment-naïve patients with chronic HCV genotype 1 infection. Hepatology58:1377A

17. Kowdley KV, Lawitz E, Poordad F, Cohen DE, Nelson DR, et al. (2014) Phase 2b trial of interferon-free therapy for hepatitis C virus genotype 1. N Engl J Med 370: 222-232.

18. Aronsohn A, Jensen D (2014) Expanding access to hepatitis C virus care: a call to deconstruct individualized therapy. Hepatology 59: 13-15.