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Editorial

The new era of hepatitis C treatment: still the tip of the iceberg?

A. GASBARRINI, F.R. PONZIANI, B.E. ANNICHIARICO, M. SICILIANO, A. CRAXÌ[1]

Gastroenterology Division, Catholic University of the Sacred Heart of Rome, School of Medicine, Rome, Italy
[1]Gastroenterology Division, University of Palermo, Palermo, Italy

The revolution of hepatitis C virus (HCV) infection treatment started in the early 1990s, with the introduction of interferon (IFN) alpha, but the best results have been achieved in the recent years. Far from the possibility to be preempted by vaccination, hepatitis C is not easy to cure in every patient. The combined therapy with pegylated-IFN (PEG-IFN) plus ribavirin (RBV), which represented the standard of care available up to now, led to suboptimal results and was almost always poorly tolerated, requiring dose reduction or treatment discontinuation. Furthermore, infection recurrence was around the corner, and patients who partially responded or did not respond to treatment had to face the frustrating concept to have no alternative therapeutic option.

The need to improve treatment results, which is particularly heartfelt when special population of patients are considered, such as liver transplant recipients and cirrhotics, pushed the scientific community to struggle for the development of new drugs. The new direct acting antivirals (DAAs) are active on specific viral components and include non-structural 3/4A (NS3/4A) protease inhibitors, nucleoside/nucleotide analogue and non-nucleoside inhibitors of the HCV RNA-dependent RNA polymerase (RdRp), inhibitors of the HCV non-structural protein 5A (NS5A), and cyclophylin inhibitors[1]. Telaprevir and Boceprevir are the first NS3/4A protease inhibitors, approved in 2011 for the treatment of genotype 1 patients[2,3]. However, the first era of DAAs will end soon, more quickly then expected. The clinical experience with Telaprevir and Boceprevir has not produced in facts fully satisfactory results. Up to 86% of genotype 1 non-cirrhotic patients may achieve a sustained virological response (SVR), (SPRINT-2, RESPOND-2, ADVANCE, REALIZE Trials[4-7]), however, strong efforts due to poor tolerability and adverse events, and 24-48 weeks of treatment are needed. Moreover, the efficacy is lower in patients experienced to treatment. Nevertheless, treatment administration is not simple and requires the intake of a number of daily pills, up to 12, in addition to RBV. Cirrhotic patients have less benefits and experience more life-threatening adverse events[8]. Data about liver transplanted patients with HCV recurrence clearly show low SVR rates, increased prevalence of acute rejection and interaction with immunosuppressants, the main factor that has made improbable their future use in these patients[9-12]. Finally, Telaprevir and Boceprevir are not approved for the treatment of genotype 2 and 3 patients, whose standard of care still remains the PEG-IFN plus RBV combination therapy.

For all these reasons, several second generation DAAs are being tested. The most promising news is that HCV treatment is clearly moving toward the burial of PEG-IFN. According to the most recent scientific reports, selected patients (and hopefully every patient in the near future) will benefit of PEG-IFN free regimens, with very good results. Three recent trials, the FISSION[13], FUSION and POSITRON[14] (Table 1) assessed the rate of SVR at 12 weeks (SVR 12) obtained after the end of treatment with the NS5B polymerase inhibitor Sofosbuvir in genotype 2 or 3 naïve, experienced to treatment or IFN intolerant patients. The results were exciting for genotype 2 patients, with SVR12 rates of at least 93%. In contrast, genotype 3 naïve patients showed more benefit from the combination of PEG-IFN plus RBV,

Corresponding Author: Antonio Gasbarrini, MD; e-mail: agasbarrini@rm.unicatt.it

Table I. Clinical trials assessing the efficacy and safety of Sofosbuvir in the treatment of HCV infection. Pegylated Interferon = PEG-IFN; Ribavirin = RBV; Adverse events = AEs; number of enrolled patients = N).

Study	Phase	Genotype	Previous treatment	Treatment groups	N	SVR12	Safety
Neutrino[13]	III	1/4/5/6	naïve	Sofosbuvir + RBV + Peg-IFN for 12 weeks	327	90% overall 92% 1a 82% 1b 96% 4 100% 5/6	Discontinuations due to AEs 5 (2%) Treatment-emergent AEs 4 (1%) AEs and laboratory abnormalities were consistent with the profile for PEG-IFN+RBV
Fission[13]	III	2/3	naïve	Sofosbuvir + RBV for 12 weeks	253	67% overall 97% 2 56% 3	Discontinuations due to AEs 3 (1%) ≥ Grade 3 AE 18 (7%)
				Peg-IFN + RBV for 24 weeks	243	67% overall 78% 2 63% 3	Discontinuations due to AEs 25 (10%) ≥ Grade 3 AE 45 (19%)
Fusion[14]	III	2/3	experienced	Sofosbuvir + RBV for 12 weeks	100	50% overall 86% 2 30% 3	Discontinuations due to AEs 1 (<1%) Treatment-emergent AEs 8 (4%)
				Sofosbuvir + RBV for 16 weeks	95	73% overall 94% 2 62% 3	
Positron[14]	III	2/3	IFN intolerant, ineligible or unwilling	Sofosbuvir + RBV for 12 weeks	207	78% overall 93% 2 61% 3	Discontinuations due to AEs 4 (2%) Treatment emergent AEs 185 (89%)
				Placebo for 12 weeks	71	0%	Discontinuations due to AEs 3 (4%) Treatment emergent AEs 55 (78%)

and lower rates of SVR12 have been reported in experienced or IFN-intolerant patients, compared to genotype 2. Preliminary experiences and phase II trials with IFN-free regimens based on DAAs combination showed encouraging results also in genotype 1 naïve and null responder patients. In particular, Sofosbuvir in combination with various DAAs, such as Daclatasvir, Ledipasvir or Simeprevir, plus RBV show excellent SVR rates, close to 100%[15-17]. However, further data are needed to confirm these results. A recent phase III trial showed that the addition of Sofosbuvir to PEG-IFN and RBV for 12 weeks could obtain excellent results in genotype 1, 4, 5 and 6 patients (92% of SVR12 in genotype 1a, 82% in genotype 1b, 96% in genotype 4 and 100% in genotype 5/6 patients; NEUTRINO trial[13], Table I). Finally, two NS3/4A protease inhibitors, Simeprevir and Faldaprevir, were also tested in genotype 1 patients in association with PEG-IFN and RBV, with inferior SVR12 rates, 80% and 79-80% respectively, than that obtained with Sofosbuvir (QUEST-1 and STARTVERSO-1 phase II trials[18,19].

Nevertheless, if data about the efficacy of the new DAAs are exciting, those regarding safety are astounding. The rate of reported adverse events is lower compared to the previous therapeutic regimens; remarkably, Sofosbuvir presents a good profile of tolerability and no hematologic toxicity[13], which represented the main limitation of combined PEG-IFN plus RBV therapy and of the first era of DAAs.

What is certain is that, about 20 years after the approval of the first treatment for hepatitis C, we have once again arrived at a starting point. New antiviral drugs, directly acting against the virus particles, are available. Some of them, namely Telaprevir and Boceprevir, disattended the initial promises, revealing low tolerability profiles and limited efficacy according to patients' genotypes and subsets (e.g. cirrhotics, liver transplanted). New all-oral, IFN-free regimens requiring short treatment duration are on the horizon. Due to the very encouraging results reported so far, the forecast of a future without HCV infection is now credible. It is unknown how much time will it take, but it is reasonable to encourage patients who have a little benefit from the treatments available so far to wait for the new incoming treatments. On the other hand, clinicians have often to deal with the willingness of their patients to be healed. The major limitation of HCV infection treatments disposable so far was the impossibility to offer to every patient the same opportunity to be treated, an opportunity that was extremely dependent on treatment tolerability and on other factors affecting the route through a favorable response. The first months of 2013 have brought great changes, but there is probably still a long way to difficult to treat go before to reach the same efficacy of treatment in every patient with hepatitis C, and what we see is just the tip of a giant iceberg.

Conflict of Interest

The Authors declare that they have no conflict of interests.

References

1) Sarrazin C, Hezode C, Zeuzem S, Pawlotsky JM. Antiviral strategies in hepatitis C virus infection. J Hepatol 2012; 56(Suppl 1): S88-100.
2) [cited 2012 July]; Available from: http://www.fda.gov/ForConsumers/ByAudience/ForPatientAdvocates/ucm256328.htm.
3) [cited 2013 July]; Available from: http://www.fda.gov/ForConsumers/ByAudience/ForPatientAdvocates/ucm255413.htm.
4) Poordad F, McCone J, Jr., Bacon BR, Bruno S, Manns MP, Sulkowski MS, Jacobson IM, Reddy KR, Goodman ZD, Boparai N, DiNubile MJ, Sniukiene V, Brass CA, Albrecht JK, Bronowicki JP; SPRINT-2 Investigators. Boceprevir for untreated chronic HCV genotype 1 infection. N Engl J Med 2011; 364: 1195-1206.
5) Bacon BR, Gordon SC, Lawitz E, Marcellin P, Vierling JM, Zeuzem S, Poordad F, Goodman ZD, Sings HL, Boparai N, Burroughs M, Brass CA, Albrecht JK, Esteban R; HCV RESPOND-2 Investigators. Boceprevir for previously treated chronic HCV genotype 1 infection. N Engl J Med 2011; 364: 1207-1217.
6) Jacobson IM, McHutchison JG, Dusheiko G, Di Bisceglie AM, Reddy KR, Bzowej NH, Marcellin P, Muir AJ, Ferenci P, Flisiak R, George J, Rizzetto M, Shouval D, Sola R, Terg RA, Yoshida EM, Adda N, Bengtsson L, Sankoh AJ, Kieffer TL, George S, Kauffman RS, Zeuzem S; ADVANCE Study Team. Telaprevir for previously untreated chronic hepatitis C virus infection. N Engl J Med 2011; 364: 2405-2416.

7) Zeuzem S, Andreone P, Pol S, Lawitz E, Diago M, Roberts S, Focaccia R, Younossi Z, Foster GR, Horban A, Ferenci P, Nevens F, Müllhaupt B, Pockros P, Terg R, Shouval D, van Hoek B, Weiland O, Van Heeswijk R, De Meyer S, Luo D, Boogaerts G, Polo R, Picchio G, Beumont M; REALIZE Study Team. Telaprevir for retreatment of HCV infection. N Engl J Med 2011; 364: 2417-2428.

8) Hezode C, Fontaine H, Dorival C, Larrey D, Zoulim F, Canva V, de Ledinghen V, Poynard T, Samuel D, Bourlière M, Zarski JP, Raabe JJ, Alric L, Marcellin P, Riachi G, Bernard PH, Loustaud-Ratti V, Métivier S, Tran A, Serfaty L, Abergel A, Causse X, Di Martino V, Guyader D, Lucidarme D, Grando-Lemaire V, Hillon P, Feray C, Dao T, Cacoub P, Rosa I, Attali P, Petrov-Sanchez V, Barthe Y, Pawlotsky JM, Pol S, Carrat F, Bronowicki JP; CUPIC Study Group. Triple therapy in treatment-experienced patients with HCV-cirrhosis in a multicentre cohort of the French Early Access Programme (ANRS CO20-CUPIC)–NCT01514890. J Hepatol 2013; May 10. [Epub ahead of print].

9) Garg V, van Heeswijk R, Lee JE, Alves K, Nadkarni P, Luo X. Effect of tlaprevir on the pharmacokinetics of cyclosporine and tacrolimus. Hepatology 2011; 54: 20-27.

10) Coilly A, Furlan V, Roche B, Barau C, Noel C, Bonhomme-Faivre L, Antonini TM, Roque-Afonso AM, Samuel D, Taburet AM, Duclos-Vallée JC. Practical management of boceprevir and immunosuppressive therapy in liver transplant recipients with hepatitis C virus recurrence. Antimicrob Agents Chemother 2012; 56: 5728-5734.

11) Kwo P GM, Lacerda M, Vinayek, R, Tector AJ, Fridell, J, Vianna R. Use of telaprevir plus PEG interferon/ribavirin for null responders post OLT with advanced fibrosis/cholestatic hepatitis C. J Hepatol 2012; 56: S86.

12) Burton JR, Everson CT. Initial experience with telaprevir for treating hepatitis C virus in liver recipients: virologic response, safety and tolerability. Am J Transplant 2012; 12: 188.

13) Lawitz E, Mangia A, Wyles D, Rodriguez-Torres M, Hassanein T, Gordon SC, Schultz M, Davis MN, Kayali Z, Reddy KR, Jacobson IM, Kowdley KV, Nyberg L, Subramanian GM, Hyland RH, Arterburn S, Jiang D, McNally J, Brainard D, Symonds WT, McHutchison JG, Sheikh AM, Younossi Z, Gane EJ. Sofosbuvir for previously untreated chronic hepatitis C infection. N Engl J Med 2013; 368: 1878-1887.

14) Jacobson IM, Gordon SC, Kowdley KV, Yoshida EM, Rodriguez-Torres M, Sulkowski MS, Shiffman ML, Lawitz E, Everson G, Bennett M, Schiff E, Al-Assi MT, Subramanian GM, An D, Lin M, McNally J, Brainard D, Symonds WT, McHutchison JG, Patel K, Feld J, Pianko S, Nelson DR; POSITRON Study; FUSION Study. Sofosbuvir for hepatitis C genotype 2 or 3 in patients without treatment options. N Engl J Med 2013; 368: 1867-1877.

15) Sulkowski MS, Rodriguez-Torres M, Reddy KR, Hassanein T, Lawitz E, Lok AS, Hinestrosa F, Thuluvath PJ, Nelson DR, Everson GT, Eley T, Huang SP, Gao M, McPhee F, Hernandez D, Sherman D, Hindes R, Symonds W, Pasquinelli C, Grasela DM. Sustained virologic response with Daclatasvir plus Sofosbuvir ± Ribavirin (RBV) in chronic HCV genotype (GT) 1-infected patients who previously failed Telaprevir (TVR) or Boceprevir (BOC). J Hepatol 2013; 58: S1417.

16) Gane E, Ding X, Pang P, McHutchison J, Stedman C. ELECTRON: 100% Suppression of viral load through 4 weeks post-treatment for Sofosbuvir + Ledipasvir (GS-5885) + Ribavirin for 12 weeks in treatment-naïve and experienced Hepatitis C Virus GT1 patients. 20th Conference on Retroviruses and Opportunistic Infections, March 3-6, Atlanta, GA, USA, 2013; 41LB.

17) Lawitz E, Rodriguez-Torres M, Younossi Z, Corregidor A, Jacobson I, Callewaert K, Symonds W, Picchio G, Lindsay K. 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 GT1 Null Responders. 20th Conference on Retroviruses and Opportunistic Infections, March 3-6, Atlanta, GA, USA, 2013; 154LB.

18) Jacobson I, Foster GR, Fried MW, Radu M, Rafalskiy VV, Moroz L, Craxì A, Peeters M, Lenz O, Ouwerkerk-Mahadevan S, Kalmeijer R, Beumont-Mauviel M. Simeprevir (TMC435) with PEGInterferon/Ribavirin for chronic genotype-1 infection in treatment-naive patients: results from QUEST-1, a phase III trial. J Hepatol 2013; 58: S1425.

19) Ferenci P, Foster GR, Zeuzem S, Sarrazin C, Moreno C, Ouzan D, Maevskaya M, Calinas F, Morano LE, Crespo J, Dufour JF, Bourliere M, Agarwal K, Forton D, Schuchmann M, Zehnter E, Nishiguchi S, Omata M, Stern JO, Datzenko Y, Scherer J, Quinson AM. Faldaprevir plus Pegylated Interferon alfa-2a and Ribavirin in chronic HCV genotype-1 treatment-naive patients: final results from STATVERSO1, a randomised double-blind, placebo-controlled phase III trial. J Hepatol 2013; 58: S1416.