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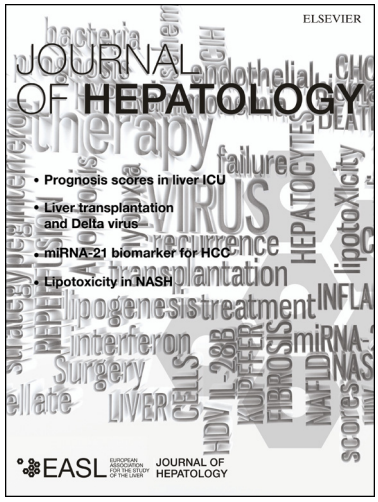

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Tarik Asselah

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Daclatasvir plus Sofosbuvir for HCV infection: An oral combination therapy with high antiviral efficacy

Tarik Asselah

Centre de Recherche sur l'Inflammation (CRI), UMR 1149 Inserm, Université Paris Diderot, Service d'Hépatologie, AP-HP Hôpital Beaujon, Clichy-France.

Keywords**:** Daclatasvir; Direct-acting antivirals; Simeprevir; Faldaprevir; Sofosbuvir.

*Corresponding author. Address: Centre de Recherche sur l'Inflammation (CRI), UMR 1149 Inserm, Université Paris Diderot, Service d'Hépatologie, AP-HP Hôpital Beaujon, Clichy-France, 100 Bd du Général Leclerc, Clichy 92110, France. Tel.: +33(0) 140875579; fax: +33(0) 147309440

E-mail address: tarik.asselah@bjn.aphp.fr

*Abbreviations***:** DAAs, direct-acting antivirals; HCV, hepatitis C virus; NI, nucleoside inhibitors; PEG-IFN, G, Genotype; pegylated-interferon; QD, once daily; RBV, ribavirin; SVR, sustained virological response.

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COMMENTARY ON:

Daclatasvir plus sofosbuvir for previously treated or untreated chronic HCV infection. Sulkowski MS, Gardiner DF, Rodriguez-Torres M, Reddy KR, Hassanein T, Jacobson I, Lawitz E, Lok AS, Hinestrosa F, Thuluvath PJ, Schwartz H, Nelson DR, Everson GT, Eley T, Wind-Rotolo M, Huang SP, Gao M, Hernandez D, McPhee F, Sherman D, Hindes R, Symonds W, Pasquinelli C, Grasela DM; AI444040 Study Group. N Engl J Med. 2014 Jan 16;370(3):211-21. doi: 10.1056/NEJMoa1306218. Copyright © (2014) Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

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Abstract: *BACKGROUND: All-oral combination therapy is desirable for patients with chronic hepatitis C virus (HCV) infection. We evaluated daclatasvir (an HCV NS5A replication complex inhibitor) plus sofosbuvir (a nucleotide analogue HCV NS5B polymerase inhibitor) in patients infected with HCV genotype 1, 2, or 3.*

METHODS: In this open-label study, we initially randomly assigned 44 previously untreated patients with HCV genotype 1 infection and 44 patients infected with HCV genotype 2 or 3 to daclatasvir at a dose of 60 mg orally once daily plus sofosbuvir at a dose of 400 mg orally once daily, with or without ribavirin, for 24 weeks. The study was expanded to include 123 additional patients with genotype 1 infection who were randomly assigned to 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). The primary end point was a sustained virologic response (an HCV RNA level of <25 IU

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per milliliter) at week 12 after the end of therapy.

RESULTS: Overall, 211 patients received treatment. 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). The most common adverse events were fatigue, headache, and nausea.

CONCLUSIONS: Once-daily oral daclatasvir plus sofosbuvir was associated with high rates of sustained virologic response among patients infected with HCV genotype 1, 2, or 3, including patients with no response to prior therapy with telaprevir or boceprevir. (Funded by Bristol-Myers Squibb and Pharmasset (Gilead); A1444040 ClinicalTrials.gov number, NCT01359644.).

Introduction

There have been major advancements in these last years with large numbers of trials with various direct-acting antivirals (DAAs) oral regimen showing increased SVR rates, favorable tolerability, and shortened treatment duration [1-5]. These DAAs target multiple viral sites: NS3/4a protease inhibitors, NS5B polymerase inhibitors, and NS5A inhibitors. HCV regimens in Phase II or III, or already approved

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in 2014 are listed in Table 1. This paper will comment on the recently published phase IIb trial with daclatasvir plus sofosbuvir for HCV Infection, reporting spectacular results [3].

Daclatasvir

Daclatasvir is a first-in-class HCV NS5A replication complex inhibitor [6]. Daclatasvir is active at picomolar concentrations *in vitro* in HCV replicons expressing a broad range of HCV genotypes and acts in an additive to synergistic fashion with interferon (IFN) and other DAAs. The resistance profile of daclatasvir reveals inhibitor sensitivity maps to the N terminus of domain 1 of NS5A. NS5A inhibitors could block hyperphosphorylation of NS5A, which is believed to play an essential role in the viral replication cycle.

Sofosbuvir

Sofosbuvir is a nucleotide analogue HCV NS5B polymerase inhibitor [7]. Polymerase inhibitors interfere with viral replication by binding to the NS5B RNA-dependent RNA polymerase. Nucleoside inhibitors (NI) mimic the natural substrates of the polymerase and are incorporated into the RNA chain causing direct chain termination. NI require conversion to an active triphosphate form. As the active site of NS5B is highly conserved, NI have generally a pan-genotypic efficacy. However, single amino acid substitutions in every position of the active site may result in loss of function of NI, but resistance to NI is typically very low as HCV has reduced fitness.

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Daclatasvir plus Sofosbuvir study design and results

In this open-label study, 44 HCV genotype 1 (G1) naïve patients and 44 HCV-G2 or G3 patients were initially randomly assigned to daclatasvir (60 mg QD) plus sofosbuvir (400 mg QD), with or without ribavirin (RBV), for 24 weeks [3] . The study was expanded to include 123 additional HCV-G1 patients who were randomly assigned to daclatasvir plus sofosbuvir, with or without RBV, for 12 weeks (82 naïve patients) or 24 weeks (41 with previous failure with telaprevir or boceprevir plus PEG-IFN–RBV)(Fig. 1A). Patients with cirrhosis were excluded.

Overall, 211 patients received treatment. Among HCV-G1 infected patients, 98% of 126 naïve patients and 98% of 41 patients who failed with protease inhibitors had an SVR at week 12 after the end of therapy (SVR12) (Fig. 1B). A total of 92% of 26 patients with HCV-G2 and 89% of 18 patients with HCV-G3 had a SVR12. All patients had an HCV RNA level of less than 25 IU/ml by week 4.

We have to be cautious regarding the results reported for HCV genotype 3, the SVR rate was of 89% after 24 weeks of daclatasvir plus sofosbuvir. This SVR appears to be similar to SVR obtained with sofosbuvir plus ribavirin given during 24 weeks in genotype 3 non-cirrhotic patients [8].

A highly efficient regimen, even in "difficult to cure" patients

Daclatasvir plus sofosbuvir was associated with high rates of SVR among patients with characteristics that were previously known to be associated with a poor response [9]. Impressively, this regimen was highly efficient in "difficult to cure" patients. All patients in whom prior failure with protease inhibitors had an SVR.

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Among these patients, 71% had virologic breakthrough or non-response, 80 were infected with subtype 1a, 98% had a non-CC *IFNL3* genotype (previously *IL28B*). Virologic breakthrough and relapse were rare and were not observed in any of the 193 patients infected with HCV genotype 1 or 2, despite pre-existing daclatasvir-resistant variants in 27 patients. Of the 5 patients infected with HCV-G1 or G2 without SVR12 after treatment, 3 had missing data at week 12 but had a SVR24 (including 1 who returned after the database lock) and 2 were lost to follow-up. Among the 18 patients with HCV-G3 infection, virologic relapse occurred in 1 of 5 patients with a pre-existing daclatasvir resistant variant, and in a second patient, who did not have pre-existing daclatasvir-resistant variants, an HCV RNA level below 25 IU/ml was detected at weeks 8 and 10. Because of low virus levels during treatment and an SVR12, the role of viral variants could not be assessed. Sofosbuvir-resistant variants were not detected in any of the patients.

Ribavirin does not appear to be useful for this DAAs combination

In this study, response rates were similar among patients treated with or without Ribavirin (RBV). These findings may reflect the antiviral potency and high resistance barrier of the daclatasvir–sofosbuvir combination and suggest that RBV is not required with every oral DAA regimen. Of course, RBV is associated with anemia, and is teratogenic, and therefore RBV-sparing regimen are desirable. However, we cannot exclude, that in cost-effectiveness strategies, RBV may have a role.

Take home messages and perspectives

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Finally, once-daily, oral treatment with daclatasvir plus sofosbuvir was associated with high SVR rates in HCV-G1, 2 or 3 naïve patients and in HCV-G1 patients with previous failure to protease inhibitors. The development of resistance appears uncommon with daclatasvir plus sofosbuvir.

Also, in the same issue of the NEJM, a phase IIb study with a 12-week DAAs combinations of ombitasvir (previously ABT-450/r, protease inhibitor), dasabuvir (previously ABT-267, NS5A inhibitor), ABT-333 (non-nucleoside polymerase inhibitor), and RBV were associated with high rates of SVR among HCV-G1 naïve patients and among patients with failure to prior PEG-IFN-RBV therapy [3]. This ombitasvir based oral regimen has shown excellent results in phase III [10-12]. The fixed dose combination of sofosbuvir and ledipasvir (NS5A inhibitor) has also demonstrated excellent results in phase III [13-15] .

Furthermore, the Cosmos study - evaluating simeprevir (protease inhibitor) plus sofosbuvir with or without RBV in GT1-naive subjects and prior null-responders - reported also impressive results [16-17]. It is a Phase 2a, randomized, open-label study that evaluated 2 cohorts of patients. Cohort 1 (n = 80) randomized prior null-responders with Metavir scores F0-F2 and cohort 2 (n = 87) evaluated prior null-responder and naïve G1 individuals with F3-F4 scores.

Data from cohort 1 demonstrated that 93% and 96% of patients with Metavir F0-F2 scores treated with simeprevir and sofosbuvir with or without ribavirin, respectively, for 12 weeks achieved SVR12.

In cohort 2, 93% of participants assigned to simeprevir/sofosbuvir either alone or with ribavirin for 12 weeks achieved SVR12; among those treated for 24 weeks, SVR12 rates were 93% and 100%, respectively.

In genotype 1a patients with the Q80K polymorphism at baseline, 89% and 83%

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achieved SVR after 12 weeks of treatment with and without ribavirin, respectively. The most common adverse events in both treatment arms were fatigue, headache, nausea, and insomnia. Two patients discontinued treatment due to adverse events.

We have to recall that several of these phase 2 studies have limitations: mainly the small number of patients limits an exact evaluation of efficacy and the possibility to detect adverse events. Also, patients with cirrhosis are excluded, and they might be less likely than those without cirrhosis to have a response, and also at higher risk of side effects. Again, HCV-G4 patients are neglected, and we have to recall that they represent around 40 million worldwide, and account for the majority of new infection, with no access to therapy, or in the best cases peg-IFN plus RBV for 48 weeks with above 40% of SVR [18].

In conclusion, these fantastic data from different published trials encourage us to remain very optimistic. We do hope that the majority of HCV infected patients will become “easy-to-cure” and there will be more facilities to access to treatment.

Conflict of interest

Tarik Asselah is a speaker and investigator for BMS, Boehringer-Ingelheim, Janssen, Gilead, Roche, and MSD.

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Table 1. HCV Regimens in Phase II or III Trials in 2014 or already approved.

Fig. 1. Study design and results. (A) The study design. The study was an open-label, phase 2, randomized trial. Treatment-naive patients (groups A through F) were randomly assigned in a 1:1:1 ratio to receive: (1) SOF for a 7-day lead-in, then DCV + SOF for 23 weeks (groups A and B), (2) DCV + SOF for 24 weeks (groups C and D) OR (3) DCV + SOF + RBV for 24 weeks (groups E and F). GT1 patients were assigned to group A, C, or E, and GT2 or GT3 patients were assigned to group B, D, or F. Additionally, 123 GT1 patients were randomly assigned in a 1:1 ratio to DCV + SOF ± RBV. Eighty-two treatment-naive patients were assigned to group G or H for 12 weeks of treatment. Forty-one prior PI failures were assigned to group I or J for 24 weeks of treatment. RBV, 1000-1200 mg/d, weight-based (GT1); 800 mg/d (GT 2/3); GT, genotype; DCV, daclatasvir; SOF, sofosbuvir (GS-7977); RBV, ribavirin; TVR, telaprevir; BOC, boceprevir; (B) Results. In treatment-naive GT1, GT2, and GT3 patients, SVR12 rates ranging from 89% to 100% were obtained in all groups receiving DCV + SOF, regardless of HCV genotype, viral subtype, treatment duration, *IL28B* genotype, or coadministration of RBV. Overall 98% (164/167) GT1 achieved SVR12. Among GT1: 98% of GT1a and 100% of GT1b patients achieved SVR12. 93% non-CC and 98% non-CC *IL28B* GT1. 94% with RBV and 98% without RBV. No patients experienced virologic breakthrough. For GT2 and GT3: 91% overall achieved SVR12. 92% of 26 of GT2 patients and 89% of 18 GT3 patients achieved SVR12. One patient with missing HCV RNA data at SVR12 later achieved SVR24 (group F). Another patient was lost to follow-up (group F). One GT3 patient relapsed (group B). One GT3 had viral breakthrough (group B). In TVR- or BOC-based therapy failures, all 40 evaluable patients receiving DCV + SOF achieved

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SVR12 (98%; 1 patient had missing data). 33 patients previously failed TVR. 8 patients previously failed BOC. No patient experienced virologic breakthrough.

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Triple Therapy:
1 DAA + PegIFN alfa/RBV

- Telaprevir
- Boceprevir
- Sofosbuvir
- Simeprevir
- Faldaprevir
- Daclatasvir
- MK 5172
- Danoprevir
- Alisporivir

IFN-Free Regimens (phase III)

- Sofosbuvir + RBV
- Sofosbuvir + Ledipasvir ± RBV
- Ombitasvir + Dasabuvir ± ABT-333 ± RBV
- Daclatasvir + Asunaprevir

IFN-Free Regimens (phase II)

- Simeprevir + Sofosbuvir
- Daclatasvir + Sofosbuvir
- Daclatasvir + Simeprevir
- Daclatasvir + Asunapreivr + BMS 791325
- MK 5172 + MK 8742 ± RBV

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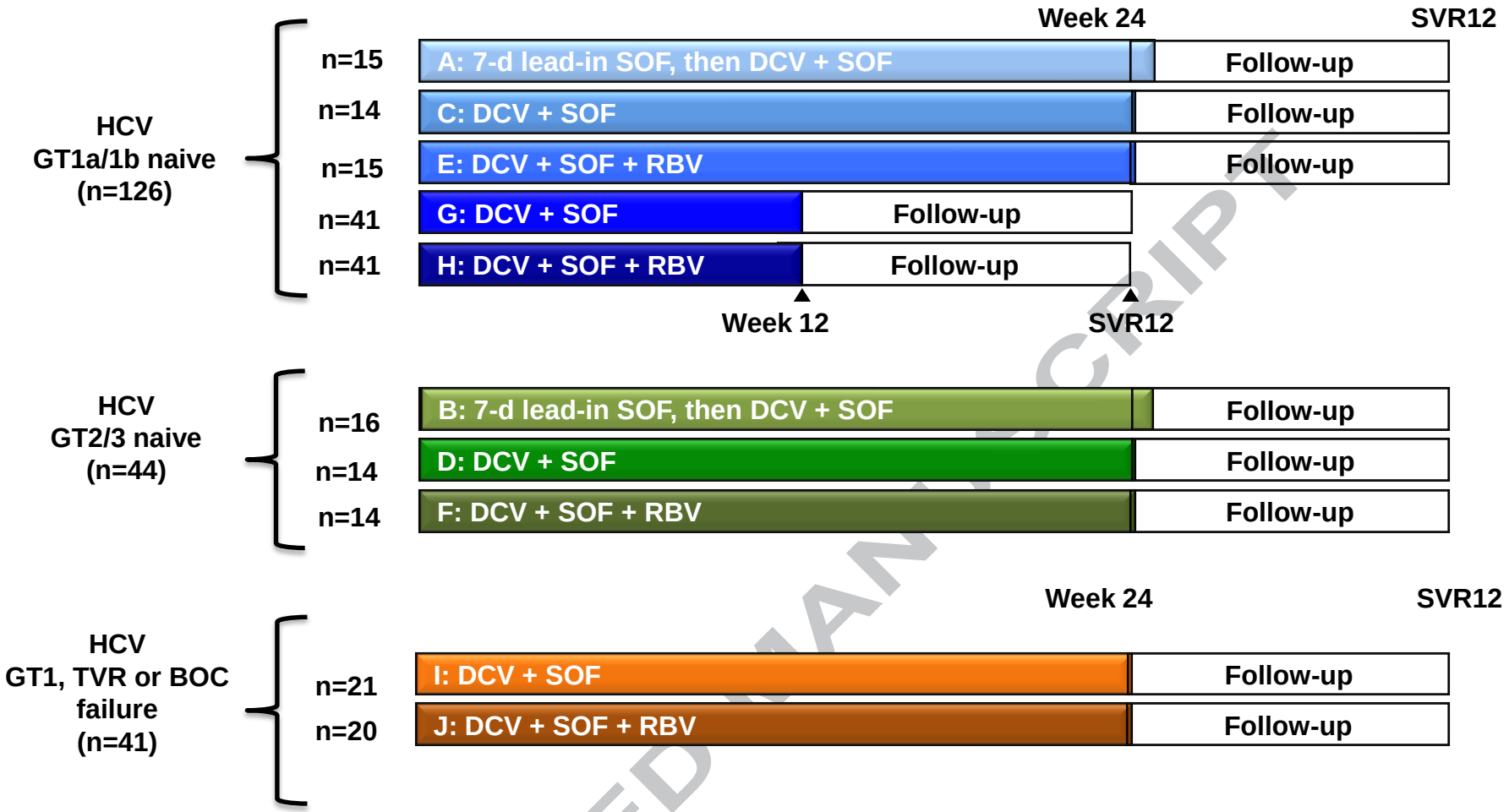

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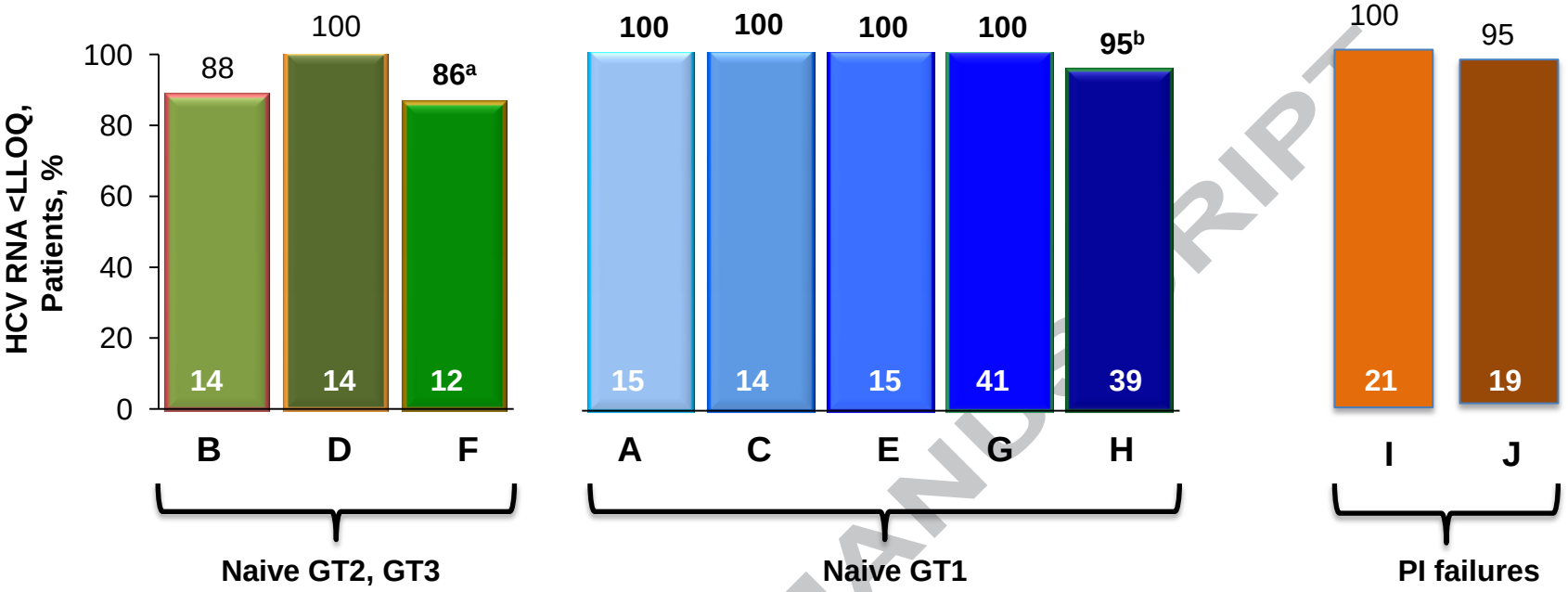

B - SOF lead-in + DCV (24 wk)

D - DCV + SOF (24 wk)

F - DCV + SOF + RBV (24 wk)

A - SOF lead-in + DCV (24 wk)

C - DCV + SOF (24 wk)

E - DCV + SOF + RBV (24 wk)

G - DCV + SOF (12 wk)

H - DCV + SOF + RBV (12 wk)

I - DCV + SOF (24 wk)

J - DCV + SOF + RBV (24 wk)