High Cure Rate With 24 Weeks of Daclatasvir-Based Quadruple Therapy in Treatment-Experienced, Null-Responder Patients With HIV/Hepatitis C Virus Genotype 1/4 Coinfection: The ANRS HC30 QUADRIH Study

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(See the Editorial Commentary by Balagopal and Thomas on pages 826–8.)

Background. Few direct anti–hepatitis C virus (HCV) agents have been studied in difficult-to-treat null responder and cirrhotic human immunodeficiency virus (HIV)-coinfected patients. Daclatasvir and asunaprevir combined with pegylated interferon/ribavirin (peg-IFN/RBV) have shown promising results in HCV-monoinfected patients.

Methods. An open-label, single-arm, phase 2 study was conducted in HIV/HCV genotype 1/4–coinfected patients who were null responders to prior peg-IFN/RBV standard therapy and on a raltegravir-based regimen with HIV RNA <400 copies/mL. They received a 4-week lead-in phase with peg-IFN/RBV, followed by 24 weeks of asunaprevir (100 mg twice daily), daclatasvir (60 mg once daily), and peg-IFN/RBV. The primary endpoint was sustained virologic response 12 weeks after the end of treatment (SVR12) using intent-to-treat analysis.

Results. Seventy-five patients were included, of whom 27 (36%) had cirrhosis. The median baseline CD4 count was 748 (interquartile range, 481–930) cells/µL. The global SVR12 rate was 96.0% (95% confidence interval [CI], 88.8%–99.2%; n = 72/75), 92.6% (95% CI, 75.7%–99.1%; n = 25/27) in cirrhotic patients, 94.6% (95% CI, 81.8%–99.3%; n = 35/37) in genotype 1 patients, and 97.4% (95% CI, 86.2%–99.9%; n = 37/38) in genotype 4 patients. Six patients (8%) stopped HCV therapy prematurely: 2 due to HCV breakthrough, 4 to adverse events (1 lung cancer, 3 infections). One patient with cirrhosis (with baseline platelet count <150 000 platelets/µL and albuminemia <35 g/L) died from multiorgan failure. Overall, 36 serious adverse events occurred in 21 (28%) patients. No HIV breakthrough was observed.

Conclusions. In HIV/HCV genotype 1/4–coinfected null responders, a 24-week regimen combining daclatasvir, asunaprevir, and peg-IFN/RBV was associated with a very high cure rate. The safety profile was acceptable, even though...
cirrhotic patients with low albuminemia and platelets should be monitored closely. This combination is a new option in this difficult-to-treat population.

Clinical Trials Registration. NCT01725542.

Keywords. HCV; HIV; daclatasvir; asunaprevir; cirrhosis.

As antiretroviral therapy (ART) has markedly reduced human immunodeficiency virus (HIV)–related mortality since 1996, mortality due to liver disease, especially related to hepatitis C virus (HCV), has increased in high-income countries [1, 2]. Chronic hepatitis C must therefore be treated effectively, as survival in patients in whom HCV has been eradicated is far better than that in patients who did not respond to anti-HCV treatment [3]. Spectacular progress has been made in HCV therapy since interferon monotherapy was introduced in 1988. Several new direct antiviral agents (DAAs) from different classes have recently shown high antiviral activity, in particular against HCV genotypes 1 and 4, which are frequent in HIV–coinfected patients. HIV coinfection (via potential interactions with ART), prior null response to standard bitherapy with pegylated interferon and ribavirin (peg-IFN/RBV), and overall cirrhosis are a cause of concern as they may affect the likelihood of cure, even with new DAAs. For example, the virologic response to prior peg-IFN/RBV in HCV genotype 1–infected patients with cirrhosis and null responders reached a maximum of 15% following retreatment with tritherapy that included first-generation protease NS3/4A inhibitors [4, 5]. However, most recent therapeutic trials with new DAAs included few HIV–infected patients with such a difficult-to-treat profile.

Daclatasvir is a selective and powerful inhibitor of the HCV NS5A replication complex [6]. It is active against several HCV genotypes, notably genotypes 1a, 1b, and 4 [6, 7]. Asunaprevir is a powerful HCV NS3 protease inhibitor active against genotype HCV 1a, 1b, and 4 [8, 9]. When combined, they induce a rapid fall in levels of HCV RNA in patients infected with genotype 1 [10]. The effectiveness of this association was shown in previous studies that included HCV genotype 1–monoinfected patients who did not respond to prior peg-IFN/RBV treatment [11–15]. However, in a proof-of-concept study in previously null-responders HCV–monoinfected patients, HCV was eradicated in only 36% of patients treated with daclatasvir plus asunaprevir bitherapy, vs 90% in those treated with a quadruple therapy that also included peg-IFN/RBV [10]. The benefit of quadruple therapy was particularly marked in patients infected with HCV genotype 1a, which is predominant in HIV–coinfected patients [16, 17]. As none of these studies included HIV–infected patients with cirrhosis, a pilot study was carried out to assess the efficacy and safety of quadruple therapy with asunaprevir, daclatasvir, and peg-IFN/RBV in HIV/HCV genotype 1 or 4–coinfected patients (including patients with cirrhosis), who were null responders to prior bitherapy with peg-IFN/RBV.

METHODS

Study Design and Participants

The ANRS HC30 QUADRIH study was an open-label, single-arm, phase 2a multicenter pilot study conducted in accordance with the Declaration of Helsinki and French law for biomedical research. It was approved by the CPP Est I Ethics Committee (Dijon, France). The protocol and its amendments were approved by the CPP Est I Ethics Committee (Dijon, France) and the French Regulatory Authority.

Patients were enrolled in 31 French clinical centers from December 2012 through July 2013. Eligible patients were aged ≥18 years, with a body weight between 40 kg and 125 kg; they had chronic HCV genotype 1 or 4 infection, detectable HCV RNA ≥1000 IU/mL at the screening visit, and were null responders to prior treatment with peg-IFN/RBV, defined by a fall in HCV RNA of <2 log10 IU/mL between day 0 of treatment initiation and week 12. They had to have been on stable ART for >1 month at the screening visit and have HIV RNA <400 copies/mL for ≥3 months and a CD4 count >200 cells/µL with CD4 rate >15%. To minimize drug–drug interactions, the ART was a raltegravir backbone combined with 2 nucleoside analogues among tenofovir, emtricitabine, abacavir, and lamivudine. Enfuvirtide could be added if needed.

Patients were classified as cirrhotic or noncirrhotic. The liver fibrosis stage was assessed with liver biopsy to establish the Metavir score and/or hepatic impulse elastometry ( Fibroscan). Cirrhosis was defined as a Metavir score of F4 on the liver biopsy or >14.5 kPa with elastometry. Patients with Child–Pugh class B or C cirrhosis or a history of decompensated cirrhosis were excluded. Other noninclusion criteria were prior HCV therapy including HCV NS3 protease inhibitors, positive Hepatitis B surface (HBs) antigenemia with hepatitis B virus (HBV) DNA >1000 IU/mL, severe heart or lung disease, transplant recipients, recent Centers for Disease Control and Prevention HIV category C opportunistic infection, any ongoing malignant disease, or addiction if it could be an obstacle to participation in the study. Hemoglobin level <90 g/L, platelet count <50 000 platelet/µL, polymuclear neutrophil count <750 cells/µL, and creatinine clearance <50 mL/minute (using the Modification of Diet in Renal Disease [MDRD] Study equation) at screening were also exclusion criteria.

Treatment Strategy

Once written informed consent had been obtained and inclusion criteria verified, patients were included and treated with...
a 4-week lead-in phase with standard bitherapy including peg-IFN alfa-2a (180 µg/week subcutaneously) and weight-based RBV (1000 mg/day when <75 kg or 1200 mg/day when ≥75 kg). Asunaprevir (100 mg twice daily) and daclatasvir (60 mg once daily) were then added at week 4, and the patients were then treated with quadruple HCV therapy for an additional 24 weeks until week 28 (end of treatment [EOT]).

Authorized supportive treatments included erythropoietin, granulocyte colony-stimulating factor, and antidepressants. The associated ART included only the allowed drugs until week 28.

HCV virologic failure was defined as the presence of HCV RNA >15 IU/mL at week 12 or thereafter (and confirmed within 2 weeks). Plasma HCV RNA was assayed on site by either Roche TaqMan 2.0 (lower limit of quantification equal to the lower limit of detection of 15 IU/mL) or Abbott RealTime 3.0 (lower limit 12 IU/mL). For each patient, the same assay was used throughout the study.

HIV viral breakthrough was defined as an HIV RNA load >400 copies/mL, confirmed by a second assay in the following 2 weeks.

Evaluation Criteria
The primary efficacy endpoint was the percentage of patients with undetectable HCV RNA at week 40—that is, 12 weeks after completion of the quadruple HCV therapy (sustained virologic response [SVR12]). Detectable HCV RNA was considered treatment failure even when levels were below the lower limit of quantification. In cases of premature discontinuation of the HCV treatment, the principal endpoint was also assessed at week 40.

Secondary efficacy endpoints included HCV virologic responses at weeks 4, 5, 6, and 8, then every 4 weeks until EOT, at EOT, and 24 weeks after treatment discontinuation (SVR24).

Safety endpoints included frequencies of adverse events (AEs), serious AEs, discontinuations due to AEs, deaths during follow-up, and HIV RNA load and immunologic evolution throughout the study.

Statistical Analysis
An intent-to-treat (ITT) analysis was performed that included all patients who initiated treatment with peg-IFN/RBV. Missing data for the primary endpoint were regarded as treatment failure.

An exact 1-sided test (significance level of .05) was used to test the null hypothesis that SVR12 was <40%, considering from previous studies (when the study was designed) that the probability of SVR after retreatment with boceprevir- or telaprevir-based HCV therapy in null responders to prior standard bitherapy would be no more than 40% [4, 5]. Assuming a response rate of 60%, 65 patients were required to achieve a power of 92% to detect such a difference in the benefits of the quadruple therapy compared with the telaprevir- or boceprevir-based strategy.

Data are presented as number and percentage or median and interquartile range (IQR) as appropriate. Associations between variables were assessed using 2-sided $\chi^2$ or Fisher exact test with a significance level of $P < .05$. All $P$ values were 2-sided, and 95% confidence intervals (CIs) of success rates were computed using binomial distribution. Statistical analyses were performed using SAS software version 9.3.

RESULTS

Baseline Characteristics of the Study Patients
Eighty-nine patients were screened, and 75 were included in the study (Figure 1). The main baseline characteristics of these patients are summarized in Table 1. Nearly half were infected with HCV genotype 1 (92% with subtype 1a). The median time between the last anti-HCV standard bitherapy and the screening visit was 48 (IQR, 30–72) months. One patient (1%) had positive HBs antigenemia (with undetectable HBV DNA on tenofovir). The median time spent on ongoing ART at screening was 2.1 (IQR, 1.3–5.2) months. ART always included raltegravir (400 mg twice daily), combined mainly with tenofovir + emtricitabine/lamivudine (n = 64 [85%]), abacavir + lamivudine (n = 7 [9%]), tenofovir + emtricitabine + enfuvirtide (n = 2 [3%]), or tenofovir + abacavir (n = 2 [3%]).

Twenty-seven patients (36%) had cirrhosis, assessed by liver elastometry in 20 and/or liver biopsy in 10 cases: 10 (37%) had a platelet count <150 000 platelets/µL and baseline albuminemia <35 g/L, and of these, 2 (7%) had both parameters below these thresholds. No significant difference (apart from fibrosis stage and HIV RNA load) was observed between cirrhotic and noncirrhotic patients (Table 1).

Virologic Response
Median HCV RNA during the lead-in phase decreased from 6.06 (IQR, 5.75–6.58) log$_{10}$ IU/mL at day 0 to 5.61 (IQR, 4.98–6.08) log$_{10}$ IU/mL at week 4 (Figure 2A). Twenty-four (32%) patients experienced a fall of >1 log$_{10}$ IU/mL HCV RNA during this phase; 8 of these had a decrease >2 log$_{10}$ IU/mL.

A sharp decrease was then observed during the first 4 weeks of quadruple therapy, with 15% (11), 37% (28), and 63% (47) of patients with undetectable HCV RNA at weeks 5, 6, and 8, respectively (Figure 2A).

The SVR12 rate was 96% (95% CI, 88.8%–99.2%; n = 72/75). Only 3 patients had detectable HCV RNA at week 40. The first 2 patients, both infected with HCV genotype 1a, one of whom was cirrhotic, experienced virologic breakthrough at week 12 and week 16 (Figure 2B). The third patient had cirrhosis (with baseline platelet count <150 000 platelets/µL and baseline albuminemia <35 g/L) and died at week 24, when HCV RNA was nevertheless undetectable.

Three other patients stopped their treatment prematurely (for cancer chemotherapy at week 19 or for AEs at weeks 24 and 25), but had undetectable HCV RNA at week 40. No relapse was observed.
In the sensitivity analyses, the SVR$_{12}$ rate in patients who experienced a $<1$ log$_{10}$ IU/mL HCV RNA decrease during the lead-in phase was 94.1% (95% CI, 83.8%–99.8%; n = 48/51). The response rate did not differ according to the HCV genotype or the presence of cirrhosis (Table 2). Neither baseline characteristics nor the virologic evolution during the lead-in phase were significantly predictive of the virologic response on therapy. SVR$_{24}$ rates were exactly the same as SVR$_{12}$ rates.

The 2 patients with virologic breakthrough at week 12 and week 16 experienced a decrease of 0.66 and 0.12 log$_{10}$ IU/mL HCV RNA, respectively, during the lead-in phase, and first reached the HCV RNA 15 IU/mL threshold on quadruple therapy at weeks 6 and 8, respectively. Although no mutations conferring resistance were detected by population sequencing at baseline, NS3 and NS5A resistance-associated mutations were detected in both patients at the time of the breakthrough: NS3 R155T/ R +D168V + NS5A R30E, and NS3 D168T + NS5A Y93N, respectively.

Safety

Four of the 75 initially treated patients stopped HCV quadruple therapy prematurely for safety reasons (Figure 1). Seventy-three patients (97%) experienced at least 1 adverse event, mainly fatigue/asthenia (n = 55), anemia (n = 26), dry skin (n = 18), decreased appetite (n = 17), diarrhea (n = 17), neutropenia (n = 8), flu-like syndrome (n = 17), headache (n = 13), and insomnia (n = 14). Thirty-six serious AEs occurred in 21 patients (Table 3): 9 cirrhotic and 12 noncirrhotic patients ($P = .44$). Only grade 3/4 thrombocytopenia was significantly more frequently observed in cirrhotic patients.

One noncirrhotic patient had to stop HCV therapy when metastatic lung cancer was diagnosed, and 3 others (all cirrhotic) because of infections: pyelonephritis, spondylitis followed by reversible renal failure, and lung abscess. One of the latter patients, with albuminemia $<35$ g/L, had already experienced pneumonitis and pyelonephritis at week 16. These resolved at week 19, but the patient then presented a lung abscess and an intracranial hematoma at week 23, which led to death 9 days later. The percentage of patients presenting infectious AEs (whatever their severity) was not significantly different between cirrhotic and noncirrhotic patients (51.9% vs 41.7%; $P = .40$).

Twenty-six (35%) patients received erythropoietin, 10 (13%) received blood transfusions, 4 (5%) received leukocyte growth factors, and 1 (1%) received platelet growth factor. Median
hemoglobin decreased to a nadir of 118 (IQR, 106–129) g/L, and 23% of the patients had hemoglobin <100 g/L at least once. Median neutrophil and platelet counts decreased to a nadir of 1289 (IQR, 980–2090) cells/µL and 104 000 (IQR, 72 000–144 000) platelets/µL, respectively. All had returned to baseline values at week 40.

Only 2 patients developed serious aminotransferase elevation (1 grade 3, 1 grade 4), which did not lead to any modification in HCV therapy and resolved spontaneously.

No significant pharmacokinetic interaction was observed between the study drugs. HIV RNA load was <50 copies/mL in all patients from week 4 to week 28 and became detectable at week 29.
40 in 4 patients (>400 copies/mL in 1 patient after modification of ART at week 34). The median CD4 count was 748 (IQR, 481–930) cells/µL at day 0; 374 (IQR, 229–528) cells/µL at week 28; and 624 (IQR, 423–798) cells/µL at week 40. The median CD4/CD8 ratio evolved from 0.95 (IQR, 0.65–1.30) at day 0 to 1.24 (IQR, 0.79–1.64) at week 28 and 0.93 (IQR, 0.57–1.49) at week 40.

**Table 2.** Sustained Virologic Response at Week 12 After Treatment Completion According to Hepatitis C Virus Genotype and Fibrosis

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Cirrhosis</th>
<th>No Cirrhosis</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotype 1</td>
<td>13/14 (92.6% [66.1%–99.8%])</td>
<td>22/23 (95.7% [78.1%–99.9%])</td>
<td>35/37 (94.6% [81.8%–99.3%])</td>
</tr>
<tr>
<td>Genotype 4</td>
<td>12/13 (92.3% [64.0%–99.8%])</td>
<td>25/25 (100% [86.3%–100%])</td>
<td>37/38 (97.4% [86.2%–99.9%])</td>
</tr>
<tr>
<td>All</td>
<td>25/27 (92.6% [75.7%–99.1%])</td>
<td>47/48 (97.9% [88.9%–100%])</td>
<td>72/75 (96.0% [88.8%–99.2%])</td>
</tr>
</tbody>
</table>

Data are presented as no./No. (% [95% confidence interval]).
The 4-week lead-in phase, albeit of no therapeutic interest in practice, allowed us to confirm that two-thirds of the patients once again experienced a genuine null response to standard bitherapy (strictly defined as a fall of no more than 1 log_{10} IU/mL HCV RNA during this phase). Sensitivity analysis confirmed the >90% SVR rate in this well-characterized population. A similar design with a 4-week lead-in with peg-IFN/RBV was also used in 2 previous ANRS trials in treatment-experienced HIV-coinfected patients receiving telaprevir or boceprevir: SVR rates in the null responders were 71% and 24%, respectively [18, 19], but none of the patients had cirrhosis.

The data for patients with no previous response and cirrhosis in HIV-coinfected patients are currently limited. Simeprevir (plus peg-IFN/RBV) was assessed in HIV-coinfected previously nonresponder patients (with an SVR rate of 57%) [20]. Simeprevir (plus peg-IFN/RBV) [20], faldaprevir (plus peg-IFN/RBV) [21], and sofosbuvir (plus ribavirin) [22] were assessed in naive HCV genotype 1–coinfected patients with cirrhosis (with SVR rates of 57%, 73%, and 65%, respectively), and sofosbuvir (plus ribavirin) in 8 naive HCV genotype 4–coinfected patients with cirrhosis (7/8 with SVR [88%]) [23]. In HIV/HCV genotype 1–coinfected cirrhotic patients, the 12-week combination of sofosbuvir + ledipasvir led to SVR rates of 94% (63/67 naive or experienced) [24] and 93% (14/15) in treatment-experienced patients treated with a 12-week combination of daclatasvir + sofosbuvir [25].

In null-responder cirrhotic HCV genotype 1–monoinfected patients, SVR_{12} rates were 87% or 95% following 12 or 24 weeks of ABT-450/r–ombitasvir + dasabuvir + ribavirin therapy [26] and 92% or 100% with 12 or 18 weeks of grazoprevir + elbasvir ± ribavirin [27], respectively. In treatment-experienced patients, SVR_{12} rates were 62% with 12 weeks of sofosbuvir + peg-IFN/RBV [28, 29], 76% with 12 weeks of sofosbuvir + simeprevir ± ribavirin [28, 29], 87% with 24 weeks of asunaprevir + daclatasvir [14], and 94% with 12 weeks of sofosbuvir + ledipasvir ± ribavirin [30]. This latter combination led to an SVR_{12} rate of 95% in HCV genotype 4–monoinfected patients, among whom some were cirrhotic and treatment experienced [31]. There are, however, few data for such populations.

In our study, the daclatasvir- and asunaprevir-based quadruple therapy led to an SVR rate >90% in 27 null-responder HIV-coinfected cirrhotic patients (infected by HCV genotype 1 or 4). No clear impact on HIV infection was observed, considering the immunovirologic evolution on HCV therapy, even though some potentially HIV-related clinical events were reported. The safety profile of this regimen was rather acceptable, with only 5% of participants discontinuing treatment for AEs, although this rate is higher than that observed with most new interferon-free combinations. Very few serious side effects were related to daclatasvir or asunaprevir. There was no significant difference between cirrhotic and noncirrhotic patients regarding

### Table 3. Main Adverse Events

<table>
<thead>
<tr>
<th>Patients With Events Until Week 52</th>
<th>All Patients (N = 75)</th>
<th>No Cirrhosis (N = 48)</th>
<th>Cirrhosis (N = 27)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any adverse event</td>
<td>73 (97)</td>
<td>46 (96)</td>
<td>27 (100)</td>
<td></td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>21 (28)</td>
<td>12 (25)</td>
<td>9 (33)</td>
<td>.44</td>
</tr>
<tr>
<td>Discontinuation due to adverse events</td>
<td>3 (4)</td>
<td>1 (2)</td>
<td>2 (7)</td>
<td>.26</td>
</tr>
<tr>
<td>Deaths</td>
<td>1 (1)</td>
<td>1 (4)</td>
<td></td>
<td></td>
</tr>
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</table>

### DISCUSSION

Six months of quadruple therapy combining daclatasvir, asunaprevir, and peg-IFN/RBV led to a very high SVR rate of 96% in patients with difficult-to-treat HIV/HCV genotype 1 and 4 coinfection (36% with cirrhosis) who had not responded to previous standard bitherapy.

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at week 40. Four potentially HIV-related events were reported: 3 oral candidiasis and 1 bacterial pneumonia.

**DISCUSSION**

Six months of quadruple therapy combining daclatasvir, asunaprevir, and peg-IFN/RBV led to a very high SVR rate of 96% in patients with difficult-to-treat HIV/HCV genotype 1 and 4 coinfection (36% with cirrhosis) who had not responded to previous standard bitherapy.
the risk of infection, even though the study was probably underpowered for this analysis. One patient died from infectious complications favored not only by cirrhosis but also by peg-IFN, and 2 others experienced serious infections leading to interruption of their treatment. All 3 of these patients had platelets (and albuminemia for 1 of them) below the thresholds recently shown to be associated with clinical risk in patients on peg-IFN–based therapy in the ANRS CO20 Compassionate Use of Protease Inhibitors in viral C Cirrhosis cohort [32]. These thresholds had not been established at the time of our study.

Only 2 genuine HCV virologic failures were observed in the study. Both of these were virologic breakthroughs after 8 and 12 weeks of the quadruple therapy, and associated with the selection of resistant variants [33, 34]. Whether or not they were linked to preexisting NS3 and NS5A minority variants, as previously reported [33, 35], was not established. On the other hand, shortening the duration of this quadruple therapy could be of interest as the few patients who prematurely stopped their HCV therapy for safety reasons reached SVR12, and as no breakthrough or relapse was observed after week 16. Questions also remain about how long and even more so whether peg-IFN/RBV—or RBV only—should or should not be associated with daclatasvir and asunaprevir in some situations, as the 2 genuine virologic failures occurred in HCV genotype 1a–coinfected patients, and considering that asunaprevir + daclatasvir bitherapy has shown high efficacy in HCV genotype 1b nonresponder, monoinfected patients [11, 12, 14, 15].

In conclusion, 24 weeks of quadruple therapy with daclatasvir, asunaprevir, and peg-IFN/RBV provided a high rate of SVR in HCV genotype 1 or 4/HIV–coinfected patients who were null responders to prior peg-IFN/RBV bitherapy. SVR rates were also high in patients with cirrhosis, even though this quadruple therapy should probably be reserved for patients in whom no other interferon-sparing regimen can be used. This quadruple combination (without the lead-in phase) is thus a valuable option in the therapeutic armamentarium, even though it is unlikely to be used as a first-line therapeutic option. Indeed, considering the expected efficacy and safety profiles of new all-oral regimens, it could be of interest as a second-line or salvage approach. It would thus be worthwhile to conduct future studies using tailored shortened durations and in patients who do not respond to first-line interferon-free therapy.

Notes

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