**Name of journal:** **World Journal of Gastroenterology**

**ESPS Manuscript NO: 12450**

**Columns: oRIGINAL aRTICLE**

***Prospective Study***

**Vitamin D in addition to peg-interferon-alpha/ribavirin in chronic hepatitis C virus infection: ANRS-HC25-VITAVIC study**

Terrier B *et al*. Vitamin D on top of Peg-IFN/ribavirin in chronic HCV infection

Benjamin Terrier, Nathanael Lapidus, Stanislas Pol, Lawrence Serfaty, Vlad Ratziu, Tarik Asselah, Vincent Thibault, Jean-Claude Souberbielle, Fabrice Carrat, Patrice Cacoub

**Benjamin Terrier, Patrice Cacoub,** Inflammation-Immunopathology-Biotherapy Department (DHU i2B), Sorbonne Universités, UPMC Univ Paris 06, UMR 7211, F-75005 Paris, France

**Benjamin Terrier,** Department of Internal Medicine, Groupe Hospitalier Cochin, AP-HP, Université Paris Descartes, Paris 5, F-75014 Paris, France

**Nathanael Lapidus, Fabrice Carrat,** INSERM, UMR\_S 1136, Institut Pierre Louis d’Epidémiologie et de Santé Publique, F-75013 Paris, France

**Nathanael Lapidus, Fabrice Carrat,** Sorbonne Universités, UPMC Univ Paris 06, UMR\_S 1136, Institut Pierre Louis d’Epidémiologie et de Santé Publique, F-75013 Paris, France

**Nathanael Lapidus, Fabrice Carrat,** Public Health Department, Saint-Antoine Hospital, AP-HP, F-75014 Paris, France

**Stanislas Pol,** Department of Hepatology, Groupe Hospitalier Cochin, AP-HP, Université Paris Descartes, Paris 5, F-75014 Paris, France

**Lawrence Serfaty,** Department of Hepatology, Hôpital Saint-Antoine, AP-HP, Université Pierre et Marie Curie, Paris 6, F-75012 Paris, France

**Vlad Ratziu,** Department of Hepatology, Groupe Hospitalier Pitié-Salpetrière, AP-HP, Université Pierre et Marie Curie, Paris 6, F-75013 Paris, France

**Tarik Asselah,** Department of Hepatology, Hôpital Beaujon, AP-HP, F-92110 Clichy, France

**Vincent Thibault,** Department of Virology, Groupe Hospitalier Pitié-Salpetrière, AP-HP, Université Pierre et Marie Curie, Paris 6, F-75013 Paris, France

**Jean-Claude Souberbielle,** Explorations Fonctionnelles, Hôpital Necker-Enfants Malades, AP-HP, Université Paris Descartes, F-75015 Paris, France

**Patrice Cacoub,** INSERM, UMR\_S 959, F-75013 Paris, France

**Patrice Cacoub,** CNRS, UMR 7211, F-75005 Paris, France

**Patrice Cacoub,** Department of Internal Medicine, AP-HP, Groupe Hospitalier Pitié-Salpêtrière, F-75013 Paris, France

**Author contributions:** Terrier B, Carrat F and Cacoub P designed research; Terrier T, Lapidus N, Pol S, Serfaty L, Ratziu V, Asselah T, Thibault V, Souberbielle JC, Carrat F and Cacoub P performed research; Terrier T, Lapidus N, Pol S, Serfaty L, Ratziu V, Asselah T, Thibault V, Souberbielle JC, Carrat F and Cacoub P analyzed data; Terrier B, Lapidus N, Carrat F and Cacoub P wrote the paper.

**Correspondence to: Patrice Cacoub, Professor,** Department of Internal Medicine, Hôpital Pitié-Salpétrière, 47-83 boulevard de l’Hôpital, 75013 Paris, France, patrice.cacoub@psl.aphp.fr

**Telephone:** +33-1-42178009  **Fax:** +33-1-42178033

**Received:** July 9, 2014 **Revised:** August 29, 2014

**Accepted:** November 18, 2014

**Published online:**

**Abstract**

**AIM:** To investigate if correction of hypovitaminosis D before initiation of Peg-interferon-alpha/Ribavirin (PegIFN/RBV) therapy could improve the efficacy of PegIFN/RBV in previously null-responder patients with chronic genotype 1 or 4 hepatitis C virus (HCV) infection.

**METHODS:** Genotype 1 or 4 HCV-infected patients with null response to previous peg-interferon-alpha and ribavirintreatment and hypovitaminosis D (less than 30 ng/mL) prospectively receivedcholecalciferol 100000 IU per week for 4 wk [from week -4 (W-4) to W0], followed by 100000 IUper month in combination with PegIFN/RBV for 12 mo (from W0 to W48). Primary outcome was the rate of early virological response defined by an HCV RNA less than 12 IU/mL after 12 wk of treatement with PegIFN/RBV.

**Results:** A total of 32 patients were included, 19 (59%) and 13 (41%) patients were HCV genotype 1 and 4, respectively. Median baseline vitamin D level was 15 ng/mL (range: 7-28).In modified intention-to-treat analysis, 29 patientswho received at least one dose of PegIFN/RBV were included in the analysis. All patients but one normalized their vitamin D serum levels. The rate of early virologic response was 0/29 (0%). The rate of HCV RNA < 12 IU/mL after 24 wk of PegIFN/RBV was 1/27 (4%). The safety profile was favourable.

**Conclusion:** Addition of vitamin D to PegIFN/RBV does not improve the rate of early virologic response in previously null-responders with chronic genotype 1 or 4 HCV infection.

© 2014 Baishideng Publishing Group Inc. All rights reserved.

**Key words:** Vitamin D; Hepatitis C virus; Chronic hepatitis; Pegylated interferon; Ribavirin

**Core tip:**Vitamin D deficiency is commonly found in patients with chronic hepatitis C virus (HCV) infection and was shown to correlate with sustained virologic response rates to Peg-interferon-alpha/Ribavirin (PegIFN/RBV) therapy. We found that the addition of vitamin D to PegIFN/RBV was well tolerated but does not improve the rate of early virologic response in previously null-responder patients with chronic genotype 1 or 4 HCV infection.

Terrier B, Lapidus N, Pol S, Serfaty L, Ratziu V, Asselah T, Thibault V, Souberbielle JC, Carrat F, Cacoub P. Vitamin D in addition to peg-interferon-alpha/ribavirin in chronic hepatitis C virus infection: ANRS-HC25-VITAVIC study. *World J Gastroenterol* 2014; In press

**Introduction**

In genotype 1 or 4 hepatitis C virus (HCV) chronic infection who failed to obtain sustained virological response (SVR) to Peg-interferon-alpha/Ribavirin (PegIFN/RBV) treatment, chances to cure are low. Previous studies showed rates of early (EVR) and SVR of roughly 7% in non-responders after retreatment with PegIFN/RBV[1,2]. Protease inhibitors specific to the HCV nonstructural 3/4A serine protease, *i.e.*, telaprevir and boceprevir, emerged as promising therapies in combination with PegIFN/RBV in chronic genotype 1 HCV infection, by significantly improving SVR rates[3-6]. Despite promising results in naïve patients, treatment of non-responderpatients to PegIFN/RBV therapy with these triple therapies results in less than 30% response rates[7]. Other promising HCV drugs combination, with or without PegIFN, very recently showed high SVR rates in previously treated patients with genotype 1 HCV infection[8]. However, side effects and/or the cost of such very effective therapeutic combinations will probably let a room for other well tolerated and cheaper therapeutic approaches.

Vitamin D deficiency is frequent in patients with chronic HCV infection. Hypovitaminosis D (≤ 30 ng/ml) was reported in three-quarters of genotype 1 patients[9] and in roughly 90% of French patients[10]. Besides its musculoskeletal effects, vitamin D seems to play a critical role in the modulation of the balance between effector and regulatory immune cells. Previous studies in genotype 1 chronic HCV infection demonstrated correlations between hypovitaminosis D and severe liver fibrosis and low virological response rates to PegIFN/RBV therapy[9]. 25-OH vitamin D in addition to PegIFN/RBV in non previously treated genotype 1 patients was also showed to significantly improve EVR(94% *vs* 48%) and SVR (86% *vs* 42%)[11].

We hypothesized that correction of hypovitaminosis D before initiation of PegIFN/RBV therapy and maintenance of an optimal vitamin D serum concentration during antiviral therapy could improve the efficacy of PegIFN/RBV therapy in null-responder patients with genotype 1 or 4 chronic HCV hepatitis.

**MATERIALS AND METHODS**

***Study design***

We designed a multicentre, prospective, open-label and uncontrolled study to assess the efficacy of the combination of vitamin D and PegIFN/RBV for retreatment of null-responder patients with genotype 1 or 4 chronic HCV infection (VITAVIC study, NCT NCT01226446).

The study protocol was approved by the institutional review boards and committees for the protection of persons at the individual study sites. The study was conducted according to the current regulations of the International Conference on Harmonisation guidelines, and the principles of the Declaration of Helsinki. All patients provided written informed consent before participating in any protocol-specific procedures. Patients were enrolled from 25 November, 2010 to 13 September, 2011.

***Participants***

To be eligible for the study, patients had to be older than 18 years, be chronically infected with genotype 1 or 4 HCV , be null-responders to a previous PegIFN/RBV therapy, have received ≥ 80% of PegIFN/RBV therapy during the previous therapy, and to have hypovitaminosis D (< 30 ng/mL). Null-responders were defined by a less than 2 log10 IU/mL decrease in HCV viral load at week 12 (W12) during the previous PegIFN/RBV course.

***Therapeutic protocol***

Patients were assigned to prospectively receive cholecalciferol 100000 IU/wk for 4 wk [from week -4 (W-4) to W0], followed by 100000 IU/per month in combination with PegIFN/RBV for 12 months (from W0 to W48). PegIFN/RBV combination was similar to the previous PegIFN/RBV course, *i.e.*, type (alpha 2a or alpha 2b) and dose of PegIFN, and dose of RBV).

***Outcomes and measurements***

The primary outcome assessment was the rate of EVR defined by an HCV RNA < 12 IU/mL after 12 wk of PegIFN/RBV.

Secondary outcome measures included (1) changes in HCV viral load after correction of vitamin D deficiency at day 0; (2) changes in HCV viral load at W4 and W12; and (3)the rate of HCV RNA <12 IU/ml at W24 and W72 (SVR).

***Safety***

Physical examination, haematological and biochemical assessments were performed at each planned visit. All reported adverse events were graded (1: mild to 4: life-threatening) using the ANRS grading system[12] and coded using MedDRA v16.1 by a trained monitor.

***Virologic, histological and immunological assessment***

HCV–RNA was detectedwith PCR assay (Abbott Molecular, Rungis, France) with a detectionlimit of 12 IU/mL. Early virologic response (EVR) was defined by a HCV-RNA < 12 IU/mL at week 12. SVR was defined by a HCV-RNA < 12 IU/mL at week 72. Patients were assessed for hepatic inflammation and fibrosis using liver biopsy and/or using serum biochemical markers. Inflammatory lesions and fibrosis on liver biopsy were graded as previously reported[13]. Inflammation and fibrosis were also assessed using ActiTestR and FibroTestR[14].HCV-RNA tests, genotyping, and histological assessment of liver biopsy were performed in each center local laboratories.

***Serum 25-OH vitamin D3 measurement***

Blood samples were immediately centrifugated at 2000 g for 10 min and serum were stored at -80 °C. Serum 25(OH)D was measured using a radio-immunossay (DiaSorin, Stillwater, MN, United States), as previously described[15].

***Statistical analysis***

Analyses of both primary and secondary outcomes were carried out in intention-to-treat, considering all patients who received at least one dose of both PegIFN/RBV and cholecalciferol. Missing values for all outcomes were imputed as failures (*i.e.*, absence of HCV RNA < 12 IU/mL and absence of changes in HCV viral load > 2 log10after correction of vitamin D deficiency, respectively). Outcomes presented as rates (EVR and SVR) were calculated with their 95%CI using the binomial exact test. Changes in HCV viral load were calculated with their 95%CI using linear mixed-effects models accounting for repeated measures.

Associations between EVR or SVR and baseline covariates or time-dependent vitamin D were explored with univariable logistic models. Associations between HCV viral load evolution and baseline covariates or time-dependent vitamin D were explored with the analysis of contrasts between visits (two-way analysis of variance on linear mixed-effects models accounting for repeated measures). *P*-values were adjusted for the multiple comparisons.

Vitamin D levels were compared with the use of the Wilcoxon signed-rank test.All analyses were performed using R software version 3.0.

The protocol was planned to include 40 patients in order to demonstrate a difference of 14% on the primary criteria, based on ahypothesized EVR rate of 21% with vitamin D in comparison to a hypothesized EVR rate of 7% in the absence of vitamin D, with an alpha risk of 5% and a power of 80%. Seven responses or more were expected to conclude to efficacy of the vitamin D strategy.

**Results**

***Characteristics of the patients***

Of the 40 planned patients, a total of 32 patients [22 men, median age 53 years (range: 25-79)] were included before the trial was stopped for futility. The statistical analysis was based on 29 patients who received vitamin D and Peg-IFN/RBV (PegIFN alpha2a in 15 patients and PegIFN alpha2b in 14patients). Flow chart of the trial is indicated in Figure 1. Patients' characteristics are summarized in Table 1.

At inclusion (W-4), median 25-OH vitamin D level was 15 ng/mL (interquartile range (IQR): 11-23), and median HCV viral load was 6.02 log10IU/mL (IQR: 5.80-6.29). During the study, 25-OH vitamin D increased significantly to 66 (58-74) at W0, 60 (50-68) at W4, and 54 (49-58) ng/mL at W12 (*P* < 0.0001) (Figure 2).

***Virologic response at W12***

Among the 29 patients analyzed, none achieved the primary endpoint at 12 weeks after initiation of Peg-IFN/RBV therapy (proportion 0%, 95%CI: 0%-11.9%).

***Evolution of HCV viral load at W0, W4 and W12***

Median HCV viral load remained stable between W-4 and W0, with viral load of 6.08 (IQR: 5.72-6.30) at W0 (*P* = 0.99 compared to W-4).At W4 of PegIFN/RBV compared to W-4, median HCV viral load significantly decreased to 5.54 (IQR: 5.19-5.83) (*P* < 0.001). Only one out of 29 patients had a reduction of HCV viral load greater than 2 log10IU/mL (proportion 3.4%, 95%CI: 0%-17.8%) at W4. No association between the evolution of HCV viral loads at W0 or W4 and baseline vitamin D levels or patients' characteristics was found.

At W12 of PegIFN/RBV compared to W4, median HCV viral load significantly decreased to 5.04 (IQR: 4.22-5.76) (*P* < 0.001). Six out of 29 (21%) patients had a reduction of HCV viral load greater than 2 log10IU/mLbetween W-4 and W12 (proportion 20.7%, 95%CI: 8%-39.7%). No association between baseline characteristics and evolution of HCV viral load at W12 was found.

***Negativation of HCV viral load at week 24 and week 72***

Six patients with a greater than 2log10IU/mL decrease at W12 were treated up to W24. Two of them achieved a virologic response and threeothershad a reduction of HCV viral load greater than 2 log10IU/mL. Since only 6 patients and 1 patient were still followed-up at W24 and W72, respectively, analyses regarding the related outcomes were not performed.

***Safety of vitamin D supplementation***

Twenty-six events in 11 patients (38%) were recorded as grade 3, and 2 events in 2 patients (7%) were recorded as grade 4. No grade 3/4 adverse event was attributable to vitamin D supplementation.

**Discussion**

Previous data in naïve genotype 1 HCV-infected patients have demonstrated correlations between hypovitaminosis D and low SVR rates to PegIFN/RBV therapy[9]. A significant improvement of EVR and SVR after vitamin D supplementation in addition to PegIFN/RBV therapy has been reported[11]. Therefore, we hypothesized that correction of hypovitaminosis D before initiation of PegIFN/RBV therapy and maintenance of an optimal vitamin D serum concentration during antiviral therapy could improve the efficacy of PegIFN/RBV therapy in null-responder patients with genotype 1 or 4 chronic HCV hepatitis. In addition, previous data demonstrated the major role of vitamin D and the vitamin D receptor (VDR) in the regulation of T cell activation bycontrollingthe T cell antigen receptor signaling[16], supporting the potential beneficial effect of vitamin D supplementation in chronic infections.

We decided to include genotype 1 or 4 HCV infected patients with a previous PegIFN/RBV therapy null response and hypovitaminosis D as they were anticipated to have very low SVR rates in case of re-treatment with PegIFN/RBV. In the present study, we demonstrate that the addition of vitamin D to PegIFN/RBV does not improve the rate of EVR in previously null-responder patients with chronic genotype 1 or 4 HCV infection. Our findings are disappointing regarding the results of previous studies and are in clear contrast with results from several observational and interventional studies. However, in contrast to the study by Abou-Mouch *et al*[11], reporting a positive effect of vitamin D supplementation in naïve genotype 1 HCV infected patients, our study assessed the benefit of vitamin D supplementation in null-responders who represent a challenging population of patients with disappointing efficacy of antiviral therapies. Along this line, we cannot exclude that our inclusion criteria, *i.e.*, null-responders, have selected patients in which the impact of adding vitamin D supplementation was negligible compared to other factors.

HCV viral load remained stable during the initial vitamin D supplementation and significantly decreased underPegIFN/RBV therapy combined with vitamin D supplementation, but without reaching our primary criteria. The evolution of serum 25-OH vitamin D level showed that our vitamin D supplementation regimen was effective and safe to obtain a significant and persistent increase of serum 25-OH vitamin D. This finding indicates that our disappointing results could not be related to serum 25-OH vitamin D insufficiency in our patients.

We must acknowledge the limits of our study. Because we aimed to analyze the efficacy of vitamin D supplementation in the era of new antiviral agents in the more challenging population of patients, *i.e.*, null responder patients, we conducted an open-label, uncontrolled study of superiority design that planned to include 40 patients. Only 32 patients were included before the trial was stopped for futility and 29 patients were analyzable for the primary endpoint. Although it could have been a limitation to draw any conclusion in case of response to vitamin D supplementation, our findings probably demonstrate the absence of interest of vitamin D in previously null-responder patients with chronic genotype 1 or 4 HCV infection. In addition, we have chosen a weekly then monthly administration of vitamin D rather than a daily dosing. Supplementation with vitamin D was previously shown to be achieved equally well with daily, weekly, or monthly dosing frequencies [17]. Therefore, our protocol was chosen to optimize adherence of long-term vitamin D supplementation, according to our habits.

In conclusion, the addition of vitamin D to PegIFN/RBV does not improve the rate of early virologic response in previously null-responder patients with chronic genotype 1 or 4 HCV infection. The lack of observed early virological response makes very unlikely the beneficial effect of vitamin D supplementation on SVR in this type of difficult to treat patients. However, vitamin D supplementation may still represent an alternative therapeutic option in naïve patients in which new specifically targeted antiviral therapy for hepatitis C would be not available or contraindicated, based on previous studies.

**Acknowledgements**

We thank Noëlle Pouget and Hubert Paniez for their assistance in collecting data.

**comments**

***Background***

In patients with genotype 1 or 4 hepatitis C virus (HCV) chronic infection who do not have a sustained virological response (SVR) to Peg-interferon-alpha/Ribavirin (PegIFN/RBV) treatment, chances to cure are low. Retreatment of previous non-responders to PegIFN/RBV therapy with triple therapies results in less than 30% SVR, indicating that other HCV drugs combination, with or without PegIFN, are needed. New HCV treatments will modify the care of chronic HCV infection in the near future in high-income countries. However, the place of such new very expensive HCV treatment combinations remains to be defined in low-income countries where cheaper alternatives have to be found.

***Research frontiers***

Vitamin D deficiency is frequent in patients with chronic HCV infection, and previous data have demonstrated correlations between hypovitaminosis D and low SVR rates to PegIFN/RBV therapy. Also, authors have reported that vitamin D in addition to PegIFN/RBV therapy for naïve genotype 1 HCV patients with chronic hepatitis improved EVR and SVR.

***Innovations and breakthroughs***

The current study investigates if the correction of hypovitaminosis D before initiation of PegIFN/RBV therapy could improve the efficacy of PegIFN/RBV in previously null-responder patients with chronic genotype 1 or 4 HCV infection.We found that the addition of vitamin D to PegIFN/RBV was well tolerated but does not improve the rate of early virologic response in previously null-responder patients with chronic genotype 1 or 4 HCV infection.

***Applications***

This study demonstrates the lack of efficacy of vitamin D supplementation in previously null-responder patients with chronic genotype 1 or 4 HCV infection. Howevern, vitamin D supplementation could still represent an alternative therapeutic option in naïve patients in which new specifically targeted antiviral therapy for hepatitis C would be not available or contraindicated.

***Terminology***

Hepatitis C virus infection is a chronic liver disease that can be complicated by cirrhosis, liver failure and liver cancer. Rates of early and sustained virologic responses in non-responders after retreatment with PegIFN/RBV is low. Besides its musculoskeletal effects, vitamin D seems to play a critical role in the modulation of the balance between effector and regulatory immune cells. Vitamin D supplementation may thus be beneficial in chronic C virus hepatitis.

***Peer review***

This study attempted to answer an important clinical question.

**REFERENCES**

1 **McHutchison JG**, Manns MP, Muir AJ, Terrault NA, Jacobson IM, Afdhal NH, Heathcote EJ, Zeuzem S, Reesink HW, Garg J, Bsharat M, George S, Kauffman RS, Adda N, Di Bisceglie AM. Telaprevir for previously treated chronic HCV infection. *N Engl J Med* 2010; **362**: 1292-1303 [PMID: 20375406 DOI: 10.1056/NEJMoa0908014]

2 **Jensen DM**, Marcellin P, Freilich B, Andreone P, Di Bisceglie A, Brandão-Mello CE, Reddy KR, Craxi A, Martin AO, Teuber G, Messinger D, Thommes JA, Tietz A. Re-treatment of patients with chronic hepatitis C who do not respond to peginterferon-alpha2b: a randomized trial. *Ann Intern Med* 2009; **150**: 528-540 [PMID: 19380853 DOI: 10.7326/0003-4819-150-8-200904210-00007]

3 **McHutchison JG**, Everson GT, Gordon SC, Jacobson IM, Sulkowski M, Kauffman R, McNair L, Alam J, Muir AJ. Telaprevir with peginterferon and ribavirin for chronic HCV genotype 1 infection. *N Engl J Med* 2009; **360**: 1827-1838 [PMID: 19403902 DOI: 10.1056/NEJMoa0806104]

4 **Hézode C**, Forestier N, Dusheiko G, Ferenci P, Pol S, Goeser T, Bronowicki JP, Bourlière M, Gharakhanian S, Bengtsson L, McNair L, George S, Kieffer T, Kwong A, Kauffman RS, Alam J, Pawlotsky JM, Zeuzem S. Telaprevir and peginterferon with or without ribavirin for chronic HCV infection. *N Engl J Med* 2009; **360**: 1839-1850 [PMID: 19403903 DOI: 10.1056/NEJMoa0807650]

5 **Poordad F**, McCone J, 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. Boceprevir for untreated chronic HCV genotype 1 infection. *N Engl J Med* 2011; **364**: 1195-1206 [PMID: 21449783 DOI: 10.1056/NEJMoa1010494]

6 **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. Boceprevir for previously treated chronic HCV genotype 1 infection. *N Engl J Med* 2011; **364**: 1207-1217 [PMID: 21449784 DOI: 10.1056/NEJMoa1009482]

7 **Asselah T**. Triple therapy with boceprevir or telaprevir for prior HCV non-responders. *Best Pract Res Clin Gastroenterol* 2012; **26**: 455-462 [PMID: 23199504 DOI: 10.1016/j.bpg.2012.09.003]

8 **Lawitz E**, Poordad FF, Pang PS, Hyland RH, Ding X, Mo H, Symonds WT, McHutchison JG, Membreno FE. Sofosbuvir and ledipasvir fixed-dose combination with and without ribavirin in treatment-naive and previously treated patients with genotype 1 hepatitis C virus infection (LONESTAR): an open-label, randomised, phase 2 trial. *Lancet* 2014; **383**: 515-523 [PMID: 24209977 DOI: 10.1016/S0140-6736(13)62121-2]

9 **Petta S**, Cammà C, Scazzone C, Tripodo C, Di Marco V, Bono A, Cabibi D, Licata G, Porcasi R, Marchesini G, Craxí A. Low vitamin D serum level is related to severe fibrosis and low responsiveness to interferon-based therapy in genotype 1 chronic hepatitis C. *Hepatology* 2010; **51**: 1158-1167 [PMID: 20162613 DOI: 10.1002/hep.23489]

10 **Terrier B**, Jehan F, Munteanu M, Geri G, Saadoun D, Sène D, Poynard T, Souberbielle JC, Cacoub P. Low 25-hydroxyvitamin D serum levels correlate with the presence of extra-hepatic manifestations in chronic hepatitis C virus infection. *Rheumatology* (Oxford) 2012; **51**: 2083-2090 [PMID: 22908327 DOI: 10.1093/rheumatology/kes209]

11 **Abu-Mouch S**, Fireman Z, Jarchovsky J, Zeina AR, Assy N. Vitamin D supplementation improves sustained virologic response in chronic hepatitis C (genotype 1)-naïve patients. *World J Gastroenterol* 2011; **17**: 5184-5190 [PMID: 22215943 DOI: 10.3748/wjg.v17.i47.5184]

12 **Hézode 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. 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; **59**: 434-441 [PMID: 23669289 DOI: 10.1016/j.jhep.2013.04.035]

13 **Bedossa P**, Poynard T. An algorithm for the grading of activity in chronic hepatitis C. The METAVIR Cooperative Study Group. *Hepatology* 1996; **24**: 289-293 [PMID: 8690394]

14 **Imbert-Bismut F**, Ratziu V, Pieroni L, Charlotte F, Benhamou Y, Poynard T. Biochemical markers of liver fibrosis in patients with hepatitis C virus infection: a prospective study. *Lancet* 2001; **357**: 1069-1075 [PMID: 11297957]

15 **Hollis BW**, Kamerud JQ, Selvaag SR, Lorenz JD, Napoli JL. Determination of vitamin D status by radioimmunoassay with an 125I-labeled tracer. *Clin Chem* 1993; **39**: 529-533 [PMID: 8448871]

16 **von Essen MR**, Kongsbak M, Schjerling P, Olgaard K, Odum N, Geisler C. Vitamin D controls T cell antigen receptor signaling and activation of human T cells. *Nat Immunol* 2010; **11**: 344-349 [PMID: 20208539 DOI: 10.1038/ni.1851]

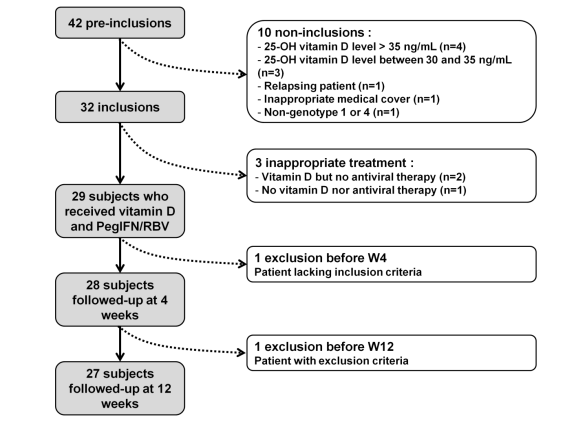
17 **Ish-Shalom S**, Segal E, Salganik T, Raz B, Bromberg IL, Vieth R. Comparison of daily, weekly, and monthly vitamin D3 in ethanol dosing protocols for two months in elderly hip fracture patients. *J Clin Endocrinol Metab* 2008; **93**: 3430-3435 [PMID: 18544622 DOI: 10.1210/jc.2008-0241]

**P-Reviewer:** Wong GLH **S-Editor:** Ma YJ **L-Editor:** **E-Editor:**

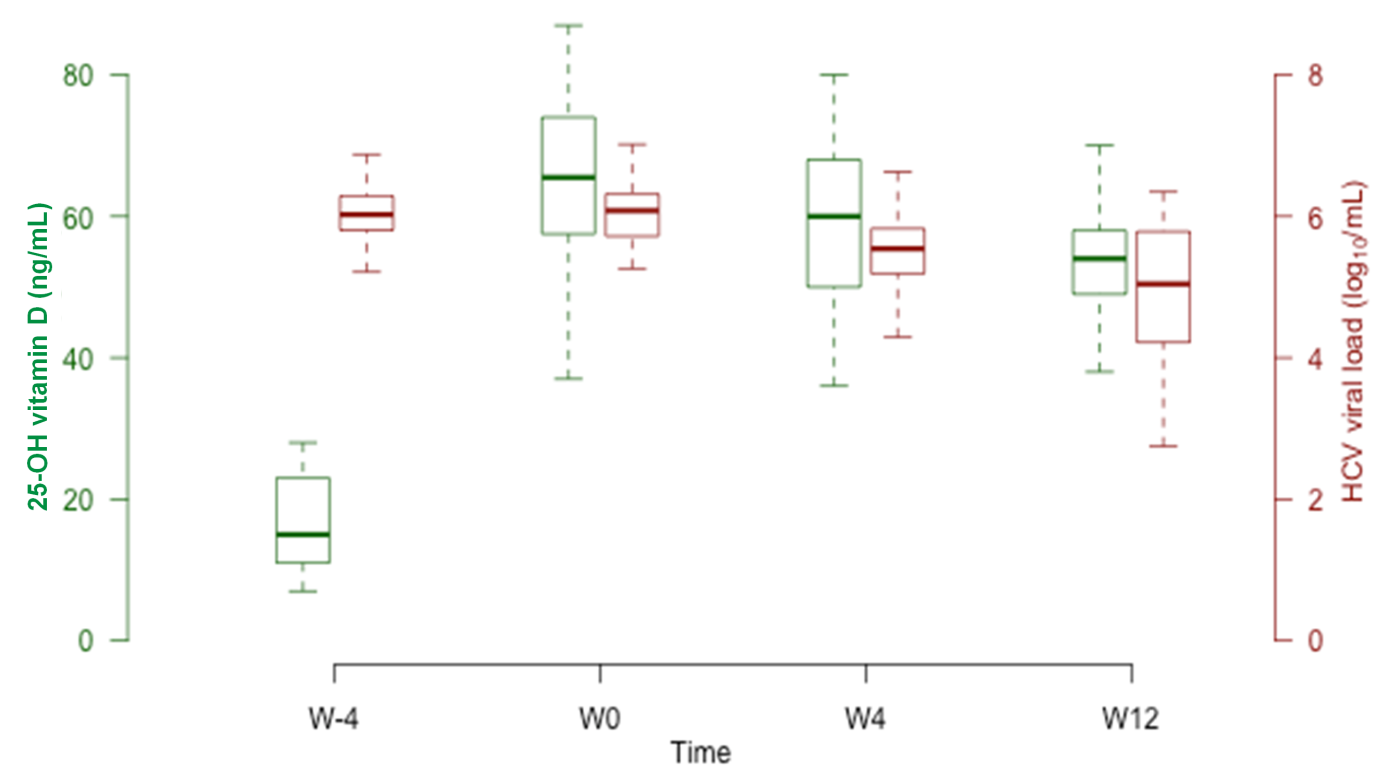
**Table 1 Characteristics of the 29 patients included in the analysis *n* (%)**

|  |  |
| --- | --- |
| **Characteristics** | **Value** |
| Age (yr) | 53.6 (50.6, 60.9) |
| Male gender | 20 (68.9) |
| HCV infection duration (yr) | 13.5 (5.6, 17.2) |
|  |  |
| **Geographic origin** |  |
| North Africa | 6 (20.7) |
| Sub-Saharian Africa | 5 (17.2) |
| West Indies | 1 (3.4) |
| Asia | 1 (3.4) |
| Eastern Europe | 1 (3.4) |
| Northern Europe | 15 (51.7) |
|  |  |
| **HCV genotype** |  |
| 1 | 8 (27.6) |
| 1a | 4 (13.8) |
| 1b | 6 (20.7) |
| 4 | 4 (13.8) |
| 4a | 5 (17.2) |
| 4c | 2 (6.9) |
|  |  |
| **Liver biopsy (*n* = 20)** |  |
| Activity Metavir score |  |
| 0 | 3 (15) |
| 1 | 9 (45) |
| 2 | 7 (35) |
| 3 | 1 (5) |
| Fibrosis Metavir score |  |
| 1 | 6 (30) |
| 2 | 7 (35) |
| 3 | 4 (20) |
| 4 | 3 (15) |
| Steatosis | 12 (60) |
|  |  |
| **Serum biomarkers (*n* = 18)** |  |
| Actitest | 0.51 (0.41, 0.66) |
| Fibrotest | 0.64 (0.47, 0.76) |
| Activity Metavir score |  |
| 0 | 1 (5.6) |
| 1 | 3 (16.7) |
| 2 | 8 (44.4) |
| 3 | 6 (33.3) |
| Fibrosis Metavir score |  |
| 0 | 3 (16.7) |
| 1 | 2 (11.1) |
| 2 | 4 (22.2) |
| 3 | 3 (16.7) |
| 4 | 6 (33.3) |
| **Fibroscan (kPa) (*n* = 20)** | 7.3 (6.2, 12.4) |
| > 10 kPa | 8 (40) |
| **Hypertension** | 7 (24.1) |
| **Dyslipidemia** | 2 (6.9) |
| **Alcohol consumption** |  |
| No | 25 (86.2) |
| Rare | 2 (6.9) |
| Regular | 2 (6.9) |
|  |  |
| **Vitamine D serum level (visit 1, ng/mL)** | 15 (11, 23) |
| **HCV viremia at inclusion (Log)** | 6.02 (5.80, 6.29) |

HCV: hepatitis C virus.



**Figure 1 Flow chart of the study.**



**Figure 2 Evolution of viral load (log10/mL) and 25-OH vitamin D (ng/mL) from W-4 to W12.**