Effects of Sofosbuvir-Based Treatment, With and Without Interferon, on Outcome and Productivity of Patients With Chronic Hepatitis C

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BACKGROUND & AIMS: **Interferon-based treatment of chronic hepatitis C virus (HCV) infection can negatively affect patient-reported outcomes (PROs) and work productivity (WP). We assessed these factors in patients with chronic hepatitis C treated with sofosbuvir and ribavirin, with or without pegylated interferon.**

METHODS: **The HCV-specific Quality of Life (Chronic Liver Disease Questionnaire-HCV version [CLDQ-HCV]), Functional Assessment of Chronic Illness Therapy-Fatigue, and Work Productivity and Activity Index: Specific Health Problem questionnaires were completed before, during, and after treatment of patients infected with HCV genotypes 2 or 3 who received sofosbuvir and ribavirin for 16 or 12 weeks (the FUSION study, n = 201) or patients infected with HCV genotype 1 who received pegylated interferon, sofosbuvir, and ribavirin for 12 weeks (the NEUTRINO study, n = 327).**

RESULTS: **Patients in each group of the FUSION study had similar PRO and WP scores at each time point (all comparisons, $P > .05$). Compared with baseline, patients had modest reductions in fatigue, HCV-specific quality of life, and WP and Activity Index scores during treatment ($P = .02$ to <.0001). However, by 4 weeks after treatment, all scores returned to baseline levels or higher. Subjects in the NEUTRINO study had greater reductions in these scores during treatment; most remained significant through 4 weeks after treatment ($P < .05$). Significant improvements in PROs were observed among patients with sustained virologic responses 12 weeks after treatment in the FUSION and NEUTRINO studies (all $P < .05$). In multivariate analyses after adjustment for confounders, interferon therapy was independently associated with worse PROs after 12 weeks of treatment.**

CONCLUSIONS: **On the basis of an analysis of 2 large clinical trials (FUSION and NEUTRINO), patient outcome and productivity are more negatively affected by the inclusion of pegylated interferon in treatment than by interferon-free regimens. Patients with sustained virologic responses 12 weeks after treatment had significant improvements in PROs in both studies.**

Keywords: CLDQ-HCV; WPAI; FACIT-F; Quality of Life; Liver Disease; Hepatitis C.

Chronic hepatitis C (CH-C) is an important cause of chronic liver disease with substantial impact on mortality, morbidity, and resource utilization.[1–3] At the individual level, CH-C is associated with fatigue leading to impairment in health-related quality of life (HRQL), which can negatively impact not only patients' well-being but also their activity and work productivity (WP).[4–12] Conversely, sustained eradication of hepatitis C virus (HCV) may improve a number of important patient-reported outcomes (PROs), including HRQL and WP.[13,14] Therefore, it is imperative that evaluation of new regimens for treatment of CH-C move beyond just reporting efficacy and safety and collect data related to important PROs such as fatigue, HRQL, and WP.[15–19] These PROs not only represent patients' experience with treatment but

Abbreviations used in this paper: **AE, activity and energy; AI, activity impairment; CH-C, chronic hepatitis C; CLDQ-HCV, Chronic Liver Disease Questionnaire-Hepatitis C version; EM, emotional; EWB, emotional well-being; FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue; FS, fatigue subscale; FWB, functional well-being; HCV, hepatitis C virus; HRQL, health-related quality of life; MCID, minimal clinically important difference; PRO, patient-reported outcome; PWB, physical well-being; SF-36, Short Form-36; SOF, sofosbuvir; SVR, sustained virologic response; SWB, social well-being; SY, systemic; WI, work impairment; WO, worry; WP, work productivity; WPAI:SHP, Work Productivity and Activity Index: Specific Health Problem.**

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also assess the indirect cost of treatment related to lower WP.

It is also important to note that despite the gradual improvement in the efficacy of interferon-containing regimens for treatment of CH-C, substantial side effects remain. These side effects lead to extensive impairment of patients' well-being and WP.[13,14,20–22] To improve the tolerability and efficacy profile of anti-HCV treatment, a number of interferon-free regimens have been developed. One such regimen includes sofosbuvir (SOF), a nucleotide NS5B inhibitor, with high efficacy and improved tolerance.[22–26] This regimen has already been shown to have a superior impact on HRQL as measured by a generic HRQL instrument, the Short Form-36 (SF-36).[27]

The purpose of the current study was to assess the impact of interferon-free and interferon-containing SOF-based regimens for treatment of CH-C on fatigue, HCV-specific quality of life, and WP.

Methods

Study Design

In the present study, we report the PRO data collected during 2 recently completed phase 3 clinical trials that evaluated SOF-based anti-HCV therapy with and without pegylated interferon.

The FUSION study was an active-control blinded study that included 12 and 16 weeks of SOF and ribavirin treatment of patients with a history of unsuccessful treatment by an interferon-containing regimen. Subjects who received 12 weeks of active treatment received an additional 4 weeks of placebo, whereas those receiving 16 weeks received active drug for the duration. The last 4 weeks of treatment were blinded. The full study design is described elsewhere.[25] For this study, the PRO questionnaires were implemented prospectively at baseline and weeks 4, 12, 16, 20, 24, and 28; however, only those with undetectable HCV RNA at week 20 were required to attend subsequent visits.

The NEUTRINO trial was a single-group open-label phase 3 study during which patients were administered a 12-week regimen of SOF, peg-interferon alfa-2a, and ribavirin. For this study, only treatment-naive patients with HCV genotype 1, 4, 5, or 6 (of whom 98% had genotype 1 or 4) were enrolled.[26] The PRO questionnaires were prospectively implemented at baseline and weeks 12, 16, and 24. However, only those with undetectable HCV RNA at week 16 were required to attend subsequent visits.

Patient-Reported Outcome Measures and Work Productivity Questionnaires

Four different questionnaires, namely Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) (a fatigue-specific questionnaire[18,19]), Chronic Liver Disease Questionnaire-Hepatitis C version (CLDQ-HCV) (an HCV-specific HRQL-related questionnaire[17]), SF-36 (a generic HRQL instrument), and Work Productivity and Activity Index: Specific Health Problem (WPAI:SHP) (a work productivity and activity questionnaire[16]) were used to assess PROs and WP in both studies. The impact of these treatment regimens as well as other SOF-containing regimens on the generic HRQL instrument (SF-36) and health utilities (SF6D) has been previously presented.[27] In this analysis, we primarily focused on assessment of fatigue, disease-specific HRQL, and WP.

It is important to note that in both FUSION and NEUTRINO, patients and investigators were blinded to the results of viral load while completing their respective PRO questionnaires.

The FACIT-F is a well-established and widely validated 40-item PRO questionnaire that assesses fatigue and its impact on daily activities and function of an individual. The scoring scheme assesses physical well-being (PWB), emotional well-being (EWB), social well-being (SWB), and functional well-being (FWB) domains as well as a fatigue subscale (FS) domain, which all add up to a total FACIT-F score. This total score ranges between 0 and 160, with 160 representing the best possible well-being. The FACIT-F questionnaire presumes a 7-day recall period.[18,19]

The CLDQ-HCV is another well-established and validated PRO questionnaire developed specifically for assessment of HRQL of individuals infected and affected by chronic liver disease, HCV in particular. It includes 4 domains, activity and energy (AE), emotional (EM), worry (WO), and systemic (SY), that, when averaged, comprise the total CLDQ-HCV score. All domains and the total score range from 1–7, with 7 representing the highest possible HRQL. In CLDQ-HCV questionnaire, subjects are asked to evaluate their health and well-being during the preceding 2-week period.[17]

The WPAI:SHP questionnaire is another validated questionnaire where participants are asked to evaluate impairment in their daily activities and work associated with a specific health problem (in this study, HCV infection). Recall period for this questionnaire is 7 days. The work impairment (WI) domain is a sum of impairment in WP due to absenteeism and impairment due to decreased productivity while working. Absenteeism is defined as productivity loss due to health-related absence from work that includes personal time off, sick days off work, duration of short-term and/or long-term work disability, or worker's-compensated days. On the other hand, presenteeism refers to reduced performance or productivity while at work because of health reasons that include the time not being on the task or decreased work quality and quantity.[28] The WP domain was assessed only for those who reported being employed at the time of completing the questionnaire. The activity impairment (AI) represents impairment in daily activities other than work, and it was assessed in all eligible participants regardless of their employment status.