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Performance and Validation of Chronic Liver Disease Questionnaire-Hepatitis C Version (CLDQ-HCV) in Clinical Trials of Patients with Chronic Hepatitis C

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ABSTRACT

Background: The hepatitis C virus (HCV) infection has tremendous clinical, health-related quality-of-life (HRQOL), and economic burden on patients and the society. To assess the comprehensive impact of HCV infection, systematic tracking of HRQOL in patients with HCV infection is important. **Objective:** The aim of this study was to systematically validate an HCV-specific HRQOL instrument, the Chronic Liver Disease Questionnaire-Hepatitis C Version (CLDQ-HCV), in patients with chronic HCV infection. **Methods:** The CLDQ-HCV has 29 items in four domains, each scored on a Likert scale of 1 – to 7. We used a large cohort of patients with HCV infection enrolled in clinical trials (N = 4142) to test internal consistency, validity, and responsiveness, and we used another cohort of untreated patients with HCV infection (N = 36) to assess test-retest reliability. **Results:** The CLDQ-HCV performed well in all the psychometric assessments. In particular, the Cronbach alphas ranged from 0.84 to 0.94 for the four domains. The item-to-own-dimension correlations exceeded 0.6 for 27 of the 29 items. Of the clinical and demographic parameters, the presence of cirrhosis and history of psychiatric conditions were discriminated best by the CLDQ-HCV (all $P < 0.0001$). The domains' correlations with similar domains of the 36-item short form health survey exceeded 0.8. The responsiveness to significant clinical outcomes such as developing treatment-induced anemia and clearance of HCV infection was notable (up to −0.70 for anemia and up to +0.85 for achieving sustained virologic response; all $P < 0.0001$). Test-retest reliability showed intraclass correlations of 0.84 to 0.93 between multiple administrations. **Conclusions:** The CLDQ-HCV is a fully validated, simple-to-administer HCV-specific instrument for patients with HCV infection that could be considered in studies of HCV-infected patients.

Keywords: hepatitis C, HRQOL, measurement tool, patient-reported outcomes, quality of life.

Introduction

Hepatitis C virus (HCV) is a systemic virus with both hepatic and extrahepatic manifestations [1–7]. In terms of liver disease associated with HCV infection, chronic hepatitis C (CH-C) is considered one of the most common and potentially devastating causes of liver disease worldwide. In fact, the clinical, economic, and patient experience impact of HCV infection has been estimated to cause tremendous burden on patients, their families, and the society [5,7]. However, HCV cure, as indicated by achieving sustained virologic response (SVR) after treatment, is associated with improvement of clinical, economic, and patient-reported outcomes (PROs) [5,8].

Historically, HCV treatment with interferon-based regimens was associated with low SVR rates and substantial side effects [9,10]. Until recently, a triple therapy combination of pegylated interferon-alpha, ribavirin, and first-generation direct-acting antiviral (DAA) agents was the standard of care for treating CH-C [11]. Postapproval data for these regimens suggested relatively low efficacy and unfavorable safety profile. Furthermore, interferon-containing regimens had a tremendously negative impact on PROs and patients' health-related quality of life (HRQOL) during treatment [12–15]. In late 2013, regimens that included second-generation DAA agents were approved, and were soon followed by the approval of all-oral regimens that had substantially higher SVR rates as well as better tolerability and cost-effectiveness profiles [16–27]. Since then, the improvement in HCV infection treatment has been clearly shown not only in terms of the superior efficacy and simplicity of the new regimens but also as a substantially improved side-effect profile, which has led to enhanced HRQOL and patient experiences [28–33].

Conflicts of interest: Z. M. Younossi is a consultant to the advisory boards of Abbvie, Intercept, Gilead Sciences, Salix, GSK, BMS, and Janssen. M. Stepanova and L. Henry have no conflicts of interest with regard to the content of this article.

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In the context of these new treatment regimens for HCV, documentation of PROs during treatment and after achieving SVR has become increasingly important to provide the most complete assessment of the effect of these treatment regimens on patients and their well-being. Although both generic and disease-specific HRQOL instruments have been shown to be useful in clinical research, it is the disease-specific instruments that are supposed to be more sensitive with regard to both the aspects of PROs that are most likely impaired in affected patients and the changes in patients' well-being associated with different stages of disease [34,35]. Thus, these disease-specific instruments are expected to be especially useful for measuring PROs during clinical trials. Nevertheless, it is important that both disease-specific and generic instruments undergo psychometric testing for reliability, responsiveness, and validity.

The Chronic Liver Disease Questionnaire-Hepatitis C Version (CLDQ-HCV) is an instrument designed specifically to assess HRQOL in patients with HCV infection [36,37]. The aim of this study was to test the CLDQ-HCV for reliability, responsiveness, and validity in patients with CH-C.

Methods

The CLDQ-HCV

The CLDQ-HCV is a self-administered questionnaire with 29 items. It was originally developed as a modified version of the CLDQ to apply specifically to patients with HCV. The details of its development and preliminary validation have been published [36–38]. In short, for its design, the original items from the CLDQ were augmented by adding the items that were expected to be pertinent to patients with HCV infection. These items were selected from various sources (generic and liver-specific instruments, interviews, and focus groups with patients with HCV infection). The initial questionnaire (item selection questionnaire) contained 77 items. An impact scores analysis and a factor analysis were performed to reduce the number of items and place the items into different domains. After the item reduction step, 40 items remained, and then, after a principle-component analysis with the selection of factors with eigenvalues greater than 1, four factors were selected. Using varimax rotation, redundancies were eliminated, and a final version of the CLDQ-HCV was developed with 29 items divided into four nonoverlapping domains: activity/energy, emotional, worry, and systemic [36].

For the CLDQ-HCV, each item was structured in an open-ended fashion and scored on a Likert scale ranging from 1 to 7: the lowest score of 1 (a problem is experienced "All of the time" or not experienced "None of the time") to the highest score of 7 (a problem is experienced "None of the time" or not experienced "All of the time"). The intermediate scores included "Most of the time," "A good bit of the time," "Some of the time," "A little of the time," and "Hardly any of the time." The four domains were calculated as an average of their constituent items, and the total score was the average of four domains. A 2-week recall period was suggested for all items [36].

Psychometric Assessment of the CLDQ-HCV

We performed an assessment of the CLDQ-HCV for validation, responsiveness, internal consistency, and test-retest reliability.

Study population: Validation cohort

For the purpose of validation of the CLDQ-HCV, we used a sample of participants from a number of phase 3 trials of new DAA drugs (sofosbuvir or a fixed-dose combination of sofosbuvir and ledipasvir) who completed the CLDQ-HCV at multiple time points before, during, and after treatment. Patients enrolled were adults (18 years or older) of all age groups, both sex, all HCV genotypes, treatment-naive or experienced, with or without compensated cirrhosis, with or without coinfection with HIV, and enrolled in North America, Europe, Australia, or New Zealand. Excluded from all trials were patients with coinfection with hepatitis B virus, patients with a history of any indication of hepatic decompensation, and patients with current pregnancy or living with a pregnant partner. Extensive medical history was collected at the time of screening for all trials' participants.

For internal consistency assessment, all time points (before, during, and after treatment) were used. For assessment of validity and discriminatory power, only one pretreatment baseline time point was used. For assessment of responsiveness, on-treatment and post-treatment time points were selected in addition to the baseline reference time point.

Study population: Test-retest reliability cohort

For the purpose of retest reliability assessment of the CLDQ-HCV, we administered the instrument 2 to 4 times to patients receiving care for their HCV infection in an outpatient clinic. Inclusion criteria were as follows: patients aged 18 years or older, chronic HCV infection for at least a year, not receiving any anti-HCV treatment at the moment or between consecutive CLDQ-HCV administrations, ability to read and understand English, and willingness to give an informed consent.

The CLDQ-HCV was self-administered by patients in an electronic form (a tablet was provided) in a clinic room before they received any information related to their present health status during two separate off-treatment visits a few weeks apart. Most of the patients also completed a paper version of the same questionnaire immediately after completion of the electronic version.

Statistical Analysis

The standard tests were used to assess test-retest reliability, internal consistency, validity, and responsiveness of the CLDQ-HCV. Only records without missing items were used.

Test-retest reliability was assessed by several methods. First, correlations between two paper-based administrations were calculated for all individual items and all the summary domains. Similarly, correlations between two electronic administrations were also calculated. Next, correlations between paper and electronic administrations were calculated. In addition, for the same pair of administrations, the distributions of differences in scores between multiple administrations were also calculated. These included the mean differences in the item values, the SDs, and the maximum absolute values of the differences; the median differences were also statistically compared with 0 by a nonparametric test for matched pairs. Finally, intraclass correlation coefficients (ICCs), which are another standard indicator of reliability, were calculated for the summary domains. A general linear model was used for each domain separately. This model used the subject identification (ID) and the administration ID (both parameters categorical; up to four administrations per subject) as two predictors of an outcome; it was expected that P values for the administration ID parameter would be substantially insignificant so that the outcome (a CLDQ-HCV domain) would be driven solely by the subject. The ICC was the ratio of between-subjects variance to the total sample variance.

Internal consistency was assessed by calculating Cronbach alphas for the CLDQ-HCV domains, and by calculating the item-to-own-domain correlations for all the CLDQ-HCV items after adjustment for overlap [39].

Validity was assessed by evaluation of the association of CLDQ-HCV scores with demographic and clinical parameters.