JOURNAL OF VIRAL HEPATITIS
JVH

Journal of Viral Hepatitis, 2013 doi:10.1111/jvh.12207

Watchful waiting: role of disease progression on uncertainty and depressive symptoms in patients with chronic Hepatitis C

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Received May 2013; accepted for publication September 2013

SUMMARY. Background and Aims: New therapies for HCV are rapidly emerging and providers are advising select patients to defer treatment and elect 'watchful waiting'. During the watchful waiting period, patients have been shown to have high rates of illness uncertainty and depression. We sought to answer the question of whether reassuring histological data (showing minimal fibrosis or no fibrosis progression over time) is associated with less illness uncertainty and depressive symptoms. Methods: This was a single-centre outpatient prospective cohort study to determine whether stage of fibrosis, fibrosis progression and reasons for treatment deferral were related to illness uncertainty and depressive symptoms in patients following watchful waiting. Results: Illness uncertainty was significantly related to depressive symptoms ($r = 0.49$, $P < 0.01$). More than half of the participants (54%) had moderate levels of uncertainty. About 40% of the participants were at risk for clinical depression (21.7% at mild to moderate risk and 18.5% at high risk). Treatment naïve subjects had lower mean scores on both the CES-D (depressive symptoms measure) and the MUIS-A (illness uncertainty measure) total score, MUIS-A Ambiguity subscale and MUIS-A Inconsistency subscale than subjects who failed treatment or were interferon intolerant or ineligible. Surprisingly, liver fibrosis stage and progression were not significantly associated with overall illness uncertainty or depressive symptoms. Conclusion: Patients with chronic hepatitis C on watchful waiting are at high risk for significant illness uncertainty and depressive symptoms. Reassuring histological data does not seem to correlate with less uncertainty or depressive symptoms.

Keywords: depression, fibrosis, hepatitis C, uncertainty, watchful waiting.

INTRODUCTION

Hepatitis C (HCV) is a worldwide public health problem, with an estimated 130–170 million people infected and approximately 4 million new infections each year [1]. Chronic hepatitis C (CHC) is the leading indication for liver transplantation and leads to more than 15 000 hepatitis C-related deaths annually in the United States [2,3]. While CHC can lead to significant morbidity and mortality, disease can progress slowly or not at all in some patients with mean time to cirrhosis of 30 years and nonprogression in almost one-third of patients [4–10].

Abbreviations: CES-D, Center for Epidemiological Studies Depression Scale; CHC, Chronic hepatitis C; HCV, Hepatitis C virus; MUIS-A, Mishel Uncertainty in Illness Scale; SD, standard deviation.

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For slow or nonprogressors, a reasonable management strategy is watchful waiting (treatment is deferred with at least annual visits with a medical provider for monitoring). This management strategy is especially relevant as rapidly emerging new therapies, still in clinical trials and not yet commercially available, are promising high cure rates with better side-effect profiles.

While advising patients on management options, clinicians weigh the individual's chance of a sustained viral response, the stage and rate of progression of their disease, the risk of severe side effects and patient preference. Informed deferral of treatment requires a discussion with the patient of the risks and benefits of watchful waiting [11]. Although CHC may progress slowly, patients are aware of potential complications. This can lead to illness uncertainty as they are unsure about what will happen to them over time with a disease that offers few cues to progression until symptoms appear.

Illness uncertainty is defined by Mishel as the inability to determine the meaning of illness-related events and occurs if the patient cannot structure a framework in which to place those events because of insufficient cues to

assign value to the experience or predict the outcome [12,13]. Uncertainty exists in illness because of unpredictable and inconsistent symptom experience, the unknown future of living with debilitating effects of an illness and/or the continual questions about the possibility of disease recurrence or exacerbation [12]. The four domains of uncertainty described by Mishel Uncertainty in Illness Scale (MUIS-A) are Ambiguity, Complexity, Inconsistency and Unpredictability (see Table 1) [14].

In addition to illness uncertainty, depressive symptoms are also common (rates of 35–59%) in patients with untreated CHC, even in the absence of active medical or psychiatric comorbidities [15,16]. Illness uncertainty and time since diagnosis were found to be related to depressive symptoms in these patients [17,18]. In a study of 135 individuals with CHC, subjects who knew their diagnosis for more than 5 years had higher scores for anxiety and depressive symptoms than those recently diagnosed [18].

Patients with CHC experience illness uncertainty and depressive symptoms, with time from diagnosis being a risk factor for depressive symptoms. The stage of fibrosis and progression of disease play a large part in the physician's management recommendation. However, there is no data on whether the histological data (stage of fibrosis and disease progression) affect illness uncertainty and depressive symptoms in patients with CHC on watchful waiting. We hypothesized that reassuring histological data (low stage of fibrosis and stable histology) would decrease illness uncertainty and depressive symptoms.

MATERIALS AND METHODS

Design

This was a single-centre prospective cross-sectional cohort study that was approved by the institutional review board. All participants provided written informed consent prior to participation in study-related procedures. Data were collected between September and March of 2011.

SUBJECTS

We enrolled adult subjects (age ≥18 years) with CHC (positive quantitative HCV RNA at any time after having a positive serum HCV antibody if treatment naïve or at least 6 months after having been treated with an interferon-based regimen) following watchful waiting. We defined watchful waiting as not receiving antiviral treatment for CHC at the time of enrolment in the study with at least annual follow-up by a medical provider and a history of treatment deferral of at least 6 months. Other inclusion criteria were a minimum of two liver biopsies at two different time points and the ability to read and write English. Patients were excluded if they had significant psychiatric histories or had received treatment with antiviral drugs within 6 months of study enrolment. Those co-infected with HIV, Hepatitis B, or any significant active medical co-morbidity were also excluded because active comorbidities might influence illness uncertainty and depressive symptoms.

Power justification

A power analysis was performed to determine the sample size for this study. For a power of 0.8 and alpha of 0.05, a sample size of 84 was needed to conduct correlational analysis for a medium effect size using data from an early study [17]. This study was not designed to examine the difference in the CES-D and MUIS-A scores between the different subgroups (treatment naïve, treatment failures, interferon intolerant/ineligible); rather, it was designed to get estimates of depressive symptoms and illness uncertainty for this population.

Measures

At the single study visit, subjects completed two validated, standardized self-report questionnaires, the modified Mishel Uncertainty in Illness Scale (MUIS-A) and the Center for Epidemiological Studies Depression Scale (CES-D). The MUIS-A is a 33-item instrument that measures uncertainty in illness [14]. It has been used to evaluate illness uncertainty in a variety of disease states including hepatitis C and has good reliability [14,17]. It includes the four subscales measuring Ambiguity, Complexity, Inconsistency and Unpredictability with the total score ranging from 32 to 160. The ranges for the subscales are as follows: Ambiguity (13–65); Complexity (7–35); Inconsistency (7–35); Unpredictability (5–25). Higher scores on the MUIS-A indicate higher levels of uncertainty. A form modified by Bailey [17] for patients with CHC on watchful waiting was used.

Table 1 Domains of Mishel Uncertainty in Illness Scale (MUIS-A)

Domain	Description
Ambiguity	Cues about the state of the illness are vague and indistinct and tend to blur and overlap
Complexity	Cues about treatment and the system of care are multiple and varied
Inconsistency	Information changes frequently or is not in accord with information previously received
Unpredictability	Lack of contingency between illness and treatment cues and illness outcome

The modified MUIS-A has reported internal consistency reliability of .90 for the total (subscale reliabilities were not reported), and in this sample, the Cronbach's alpha for the total MUIS-A was .84; reliabilities for subscales were as follows: ambiguity (Cronbach's alpha = 0.92), complexity (Cronbach's alpha = 0.74), inconsistency (Cronbach's alpha = 0.84) and unpredictability (Cronbach's alpha = 0.63). The CES-D is a 20-item instrument designed to measure current level of depressive symptomology [19]. Scores range from 0 to 60, with scores 16 to 23 indicating mild to moderate risk for clinical depression and scores greater than 23 indicating high risk [19,20]. The CES-D has reported internal consistency reliability of 0.88–0.92 for the total scale (Radloff, 1977), and in this sample, it was 0.80.

Additional data

We collected additional data using a patient questionnaire and chart review form and these included age, gender, race, ethnicity, educational level, time from the diagnosis of HCV, stage of fibrosis, fibrosis progression, reason for watchful waiting, risk factors for CHC infection, concurrent antidepressant use and concurrently under the care of a therapist for depression. Liver fibrosis was staged using the Metavir system [21]. Fibrosis progression was defined as an increase in fibrosis stage between the two most recent liver biopsies and collected as a dichotomous variable. Reason for watchful waiting was obtained by chart review and subject report and categorized into treatment failure, treatment naïve and interferon intolerant or ineligible. The treatment failure group included nonresponders, partial responders and relapsers. Interferon intolerant or ineligible subjects had treatment stopped due to intolerable side effects of interferon or had a contraindication to interferon therapy. Ninety-five per cent of the subjects enrolled were being treated by a single hepatologist.

Statistical analysis

The statistical software IBM/SPSS 19 Base was used to calculate descriptive statistics and correlations (IBM, Chicago, IL, USA). Pearson correlation coefficient (r) was calculated between MUIS-A (including subscales) and CES-D scores. Point bi-serial correlations were calculated between MUIS-A scores, CES-D scores and fibrosis progression when progression was a dichotomous variable. Spearman's correlations were calculated for progression when the degree of progression from one stage of fibrosis to another was rank ordered from −2 to 3. Regression by two stages would be categorized as −2, by 1 stage would be −1. No change in the stage of fibrosis would be categorized as 0. Progression by 1 stage would be categorized as 1, by 2 stages as 2, by 3 stages as 3. Spearman's correlations were calculated between MUIS-A scores, CES-D scores and stage of fibrosis because stage of fibrosis was ordinal. If data were non-normal, and an assumption of the statistic was normality, data were transformed using the Johnson family of transformation.

RESULTS

Sample characteristics

The ninety-two subjects enrolled in this study were mostly male (64%), White (83%), non-Hispanic (99%), with at least a high school diploma as their highest level of education (94%) (See Table 2). The mean age for patients was 56.10 years (SD = 7.40) with a range of 24–74 years. Sixty-four of the subjects failed treatment previously (69.6%), while 19 subjects (20.7%) were treatment naïve, and nine subjects (9.8%) were interferon intolerant or ineligible (See Table 3). The mean time between the two biopsies was 4.45 years (range 1.08–8.59 years).

Illness uncertainty

This cohort of participants with CHC on watchful waiting had a moderate level of illness uncertainty. The mean MUIS-A score was 86.45 (SD 13.84; range: 37–117), which indicates a moderate level of illness uncertainty (See Table 3). Fifty participants (54%) had uncertainty scores of 80 or greater, indicating moderate levels of uncertainty.

Depressive symptoms

The mean CES-D was 18.87 (SD 8.4; range: 0–47), indicating a mild to moderate level of depressive symptoms (See Table 3). There were 37 subjects (40.2%) who had a

Table 2 Subject characteristics

	Mean (range)
Age	56.1 years (24–74)
Gender N (%)	
Male	59 (64.1%)
Female	33 (35.9%)
Ethnicity N (%)	
Hispanic	1 (1.1%)
Non-Hispanic	91 (98.9%)
Race N (%)	
Black	5 (5.5%)
White	83 (91.2%)
Other	3 (3.3%)
Education level N (%)	
Some high school	5 (5.5%)
High school diploma	51 (56.0%)
Bachelors degree	19 (20.9%)
Masters degree	12 (13.2%)
Doctorate	4 (4.4%)

Table 3 Mean MUISA and CESD scores by group

	Total	Treatment failures	Treatment naive	Interferon intolerant/ineligible
N (%)	92 (100%)	64 (69.6%)	19 (20.7%)	9 (9.8%)
MUIS-A Mean (SD)				
Total	86.45 (13.84)	87.33 (14.40)	83.58 (11.08)	86.22 (15.60)
Ambiguity	32.29 (10.49)	32.97 (9.97)	29.84 (11.58)	32.67 (12.21)
Complexity	26.63 (4.26)	26.50 (4.03)	26.5 (5.23)	27.78 (3.93)
Inconsistency	13.95 (4.90)	14.48 (4.85)	12.42 (4.25)	13.33 (6.25)
Unpredictability	13.58 (3.58)	13.38 (3.68)	14.79 (3.55)	12.44 (2.42)
CES-D	18.87 (8.39)	19.31 (8.97)	17.26 (6.16)	19.11 (8.65)

SD, standard deviation.

CES-D score of 16 or greater, indicating an increased risk for clinical depression. Of these 37 subjects, 20 subjects (21.7%) had scores of 16–23, indicating mild to moderate risk for clinical depression, and 17 subjects (18.5%) had scores greater than 23, indicating high risk.

Treatment naïve subjects had lower mean scores on both the CES-D and the MUIS-A total score, MUIS-A Ambiguity subscale and MUIS-A Inconsistency subscale than subjects who failed treatment or were interferon intolerant or ineligible (See Table 3). These were not evaluated with tests of statistical significance.

Correlations

The total MUIS-A and the Ambiguity and Inconsistency subscale scores were significantly correlated with the CES-D score ($r = 0.49$, 0.51, 0.36; $P < 0.01$, <0.01, <0.01, respectively) (See Table 4). CES-D and MUIS-A (total and all the subscales) were not significantly correlated with time from the diagnosis of HCV or fibrosis progression, measured as a dichotomous variable (See Table 4), nor was the ranked change in stage of fibrosis significantly correlated with depressive symptoms. Ranked change in stage of fibrosis was significantly correlated with the MUIS-A unpredictability subscale (See Table 4). Stage of fibrosis was significantly correlated with the MUIS-A Complexity subscale, but not with CES-D, the total MUIS-A score or any of the other subscales.

DISCUSSION

We found a substantial rate of illness uncertainty (54%) and depressive symptoms (40%) in our cohort of patients with CHC on watchful waiting, consistent with the prior studies [15,16]. Surprisingly, the histological data did not correlate with overall illness uncertainty and depressive symptoms. The stage of fibrosis was significantly related to the Complexity subscale of illness uncertainty, but not to the overall illness uncertainty score or other illness uncertainty subscales. Clinicians often make recommendations for the patient to defer treatment and offer reassurances about their minimal and/or stable disease based on liver biopsy. However, reassuring histological data do not seem to lower the patients' feelings of illness uncertainty or

Table 4 Correlations between diagnosis and fibrosis variables, and CES-D and MUIS-A

	CES-D	MUIS-A Total	MUIS-A Ambiguity	MUIS-A Inconsistency	MUIS-A Complexity	MUIS-A Unpredictability
Time from Diagnosis	0.07	0.15	0.16	0.19	−0.08	−0.04
Fibrosis progression	−0.15	0.04	0.05	0.11	−0.01	−0.15
Fibrosis change (rank ordered ρ)	−0.4	0.04	0.05	0.09	0.02	−0.21*
Stage of fibrosis (ρ)	0.15	0.03	0.02	−0.03	0.22*	0.08
MUIS-A Total	0.49**					
MUIS-A Ambiguity	0.51**					
MUIS-A Inconsistency	0.36**					
MUIS-A Complexity	−0.07					
MUIS-A Unpredictability	−0.01					

ρ, Spearman's rho.
*$P < 0.05$; **$P < 0.01$.

depressive symptoms. Recognizing this paradox is important for clinicians and points to the need for additional research about how patients process relevant medical information.

We confirmed the previous finding of the association between overall illness uncertainty and depressive symptoms in patients with CHC following watchful waiting with a similar mean uncertainty score (86.5 *vs* 87.1) [17]. Bailey *et al.*[17] found that patients with CHC following watchful waiting experience depressive symptoms associated with illness uncertainty. In his study on uncertainty, symptoms, and quality of life in patients with CHC, three constructs of illness uncertainty, Ambiguity, Inconsistency and Complexity, were significantly related to depressive symptoms. Unpredictability, another construct of illness uncertainty, was not significantly related to depressive symptoms [17]. In our study, we also found the Ambiguity and Inconsistency subscale scores to be positively significantly correlated with the CES-D scores, indicating a strong positive relationship between inconsistency and ambiguity in illness and depressive symptoms (See Table 3). The high rates of depressive symptoms and the correlation of the depressive symptoms to illness uncertainty point to the importance of illness uncertainty (especially the Ambiguity and Inconsistency components) as a possible target for intervention.

This correlational study was not designed to show clear cause and effect. While illness uncertainty is correlated with depressive symptoms, it is unclear whether illness uncertainty contributes directly to depressive symptoms or whether those who have depressive symptoms have higher levels of illness uncertainty because of their depressed disposition. It may be the case that those patients with depressive symptoms have higher levels of illness uncertainty and that the correlations are related to personality traits or neuropsychiatric attributes than knowledge of the disease or the extent of disease present. An intervention study to reduce illness uncertainty might help elucidate the causal relationship between illness uncertainty and depressive symptoms if the reduction of illness uncertainty resulted in decreased depressive symptoms. Measuring illness uncertainty before and after liver biopsy, and after treatment might also provide insight into the causal relationship of the two variables.

There is also data showing that patients with CHC experience cognitive impairment (in the areas of concentration, working memory, sustained attention and processing speed) and have cerebral metabolite abnormalities suggestive of frontal–subcortical dysfunction [22–24]. Patients with CHC were found to be impaired on more cognitive tasks than those who cleared hepatitis C, suggesting a direct viral effect. While these studies looked at cognitive function rather than depressive symptoms and illness uncertainty, they raise the questions of whether the depressive symptoms and illness uncertainty seen in patients with CHC might be from a direct viral effect and whether clearance of hepatitis C leads to decreased depressive symptoms and illness uncertainty because of its direct affect on the brain. Answering these questions would require brain imaging to be part of future studies.

Recent new information regarding medication advancements in hepatitis C treatment likely contributed to higher scores on the Inconsistency subscale of the MUIS-A for this population as new therapies were emerging at the time data were collected for this study. Advancement in treatment for HCV-infected patients probably raised concerns about the possible success or failure of viral eradication for this cohort, questions about the possibility of additional treatment advances, and concerns in general regarding the timing of treatment, the possibility of side effects of treatment and the duration of treatment. Some patients may have experienced more uncertainty, while others may have experienced less because hope for cure might have influenced uncertainty levels in both directions.

While the study was not powered to detect statistically significant differences in the scores between the different subgroups (reasons for deferral), the treatment naïve patients had lower mean scores on both the illness uncertainty and depressive symptoms scales. Additional studies with larger samples are required to explore the influence of the reasons for deferral on illness uncertainty and depressive symptoms.

There are no other studies available to provide insight into why the factors other than illness uncertainty might not have been significant in this population. More work is needed to determine the factors that cause and ameliorate patients' feelings of illness uncertainty and depressive symptoms while in watchful waiting. Qualitative studies designed to understand illness uncertainty in patients with hepatitis C on watchful waiting could provide insight into the illness experience of patients in this population. This insight can, in turn, help researchers design intervention studies using the Theory of Uncertainty in Illness, as has been carried out in populations who have other diseases [25–29]. We also hope to reassess illness uncertainty and depressive symptoms in this cohort of patients on follow-up after they have been treated to determine whether those who are cured have a decrease in their illness uncertainty and depressive symptoms.

With more efficacious and tolerable therapies on the horizon, many patients are advised to defer treatment. Given this population's high risk for illness uncertainty and depressive symptoms, part of the informed deferral process should be assessment for illness uncertainty and depressive symptoms.

In conclusion, we found that reassuring histological data were not correlated with less depressive symptoms and illness uncertainty in patients with CHC on watchful waiting. Clinicians who advise patients to defer treatment should be aware of the possibility of the symptoms and address them.

ACKNOWLEDGEMENTS AND DISCLOSURES

This work was conducted with support from Harvard Catalyst | The Harvard Clinical and Translational Science Center (National Center for Research Resources and the National Center for Advancing Translational Sciences, National Institutes of Health Award 8UL1TR000170-05 and financial contributions from Harvard University and its affiliated academic healthcare centres). The content is solely the responsibility of the authors and does not necessarily represent the official views of Harvard Catalyst, Harvard University and its affiliated academic healthcare centres, or the National Institutes of Health.

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