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Clinical Outcomes of Hepatitis C Treated with Pegylated Interferon and Ribavirin via Telemedicine Consultation in Northern California

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Abstract

Background—Patients in rural communities are less likely to receive treatment for their hepatitis C (HCV) infection. Telemedicine (TM) consultation can close the gap of access to specialists in remote and under-served areas.

Aim—To determine treatment response and side-effect profiles among HCV patients treated with pegylated interferon and ribavirin via TM consultation in different rural locations in Northern California compared with patients treated in traditional hepatology office visits.

Methods—We performed a retrospective analysis of 80 HCV patients treated at different TM sites (TM, $n = 40$) and at the University of California Davis Hepatology Clinic (HC, $n = 40$) between 2006 and 2010, comparing baseline characteristics and clinical outcomes.

Results—At baseline, response to therapy was similar for patients in both groups. Sustained virological response (SVR) was similar in both groups (TM: 55 vs. HC: 43 %; $p = 0.36$), and a higher proportion of patients treated via telemedicine completed treatment (TM: 78 vs. HC: 53 %; $p = 0.03$). TM patients had many more visits per week of therapy (TM: 0.61 vs. HC: 0.07; $p < 0.001$). Neutropenia, GI side effects, fatigue, depression, weight loss, insomnia, and skin rash were

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similar in both groups. For HC patients incidence of anemia was significantly higher (53 %) than for the TM group (25 %; $p = 0.02$).

Conclusions—The two groups had equivalent SVR. For the TM group therapy completion was superior and incidence of anemia was lower. This initial study suggests that, as a group, patients with HCV, can be safely and effectively treated via telemedicine.

Keywords

Telemedicine; Hepatitis C; Interferon; Ribavirin; Medically under-served areas; Rural communities

Introduction

Chronic hepatitis C infection is a significant public health problem with a large cost burden to society. Recently, HCV has surpassed HIV as a cause of mortality in the United States [1]. Hepatitis C infection is the most common blood-borne infection in the US, with an estimated 3.2 million chronically infected people nationwide [2]. Chronic hepatitis C is the leading cause of chronic liver disease and a leading cause of hepatocellular carcinoma (HCC) in the US, with an estimated 8,000–13,000 deaths annually [2–4].

Injection drug use continues to be the leading risk factor for hepatitis C infection. Peak prevalence occurs among adults aged 40–49 years, with individuals of lower socio-economic status and African Americans bearing a disproportionally high burden of chronic hepatitis C infection [2, 4]. Most liver transplants in this country occur among patients with cirrhosis as a result of hepatitis C infection [5, 6]. It is estimated that the associated total direct and indirect cost of hepatitis C-associated cirrhosis and HCC is [$5 billion each year in the US [7].

In California alone, an estimated 600,000 persons have been exposed to HCV and approximately 450,000 Californians are living with chronic hepatitis C infection. Racial disparity in the incidence of infection is such that infection among African Americans is the higher than among other racial and ethnic groups. The prevalence of hepatitis C infection among African Americans living in California is estimated at 3.2 %, among Latinos, 2.1 %, and among Caucasians, 1.5 % [8].

Studies have shown that HCV-infected individuals without access to a specialist are less likely to receive treatment [9]. This is significant from clinical and public health perspectives because, on average, 50 % of patients treated with combination pegylated interferon and ribavirin achieve long-term remission with resulting liver-related mortality that approximates that of the general population [10–12]. With newly available triple therapy, which includes protease inhibitors, sustained virological response (SVR) for all HCV genotypes has improved significantly to an estimated 60–80 % cure [13, 14].

Telemedicine consultation offers the potential to increase access to specialists of those in remote and underserved areas; this would benefit chronic HCV patients by providing primary care providers (PCPs) and patients in rural communities with access to diagnosis and treatment. Rural communities often lack access to specialty care [15, 16] and,

increasingly, PCPs in remote areas are being called upon to diagnose and treat patients with HCV. Unfortunately, many are unprepared for evaluation and management of the complexity of patients with chronic HCV. Consequently, practice patterns among rural PCPs are highly variable for HCV treatment. For example, few rural practitioners have experience managing treatment side effects of pegylated interferon and ribavirin (treatment-induced depression, neutropenia, thrombocytopenia, anemia, GI side effects, rash) or the complex mental health and substance abuse issues that are common among patients with hepatitis C infection [17]. Given that optimum management of chronic HCV requires consultation with highly trained specialists, it is promising to note that PCPs in New Mexico were able to treat HCV patients with similar outcomes after receiving training by specialists via videoconferencing [17].

In the last 10 years, we have provided consultations to patients with HCV via telemedicine at different locations throughout California. Our telemedicine sites have included primary clinics in rural areas with high prevalence of HCV and low socioeconomic status, and in correctional facilities.

Patients and Methods

Cohort

We performed a retrospective analysis using standard chart review of all HCV patients seen by a single hepatologist physician at five telemedicine sites in Northern California and at the University of California Davis Hepatology Clinic between 2006 and 2010. We identified a total of 40 eligible HCV patients who initiated treatment with this physician at the UC Davis Hepatology Clinic during this time period. We subsequently identified the first 40 eligible patients who initiated treatment via TM consultation, in chronological order, by use of a convenience sample method, to obtain an equivalent sample size in the TM group. The overall number of patients for the TM group was significantly larger; at the time of the data collection, however, a significant number of these patients had not yet completed therapy and SVR data were unavailable. For this reason, these additional patients were not included in this initial study. Inclusion in the study required patients to be between the ages of 18 and 75 years, have documented HCV infection via PCR, be treatment naïve, and be referred to the specialist for HCV treatment by a primary care provider.

For safety and ethical reasons and to reduce possible confounding, patients with active substance use, a psychiatric diagnosis of uncontrolled clinical depression, who were residents of correctional facilities, had co-infection with HBV or HIV, and/or had an underlying malignancy were excluded from the study.

For study subjects, we collected data that have been shown in the literature to potentially affect treatment outcomes, including age at initiation of therapy, gender, ethnicity, BMI, hepatitis C genotype, metavir stage of fibrosis, and HCV RNA level at initiation of therapy.

Use of Telemedicine Consultation

Telemedicine is the use of high-speed, wide bandwidth transmission of digitized signals in conjunction with computers to provide an audio-visual interaction in real time between a

patient and physician who are physically separated. Telemedicine offers unique opportunity for realtime interactions among a three individuals (Fig. 1): the patient who is in need of specialty care, the PCP who actively participates during the consultation, and the specialist who provides consultation services and education in management to both patient and PCP simultaneously. The sequence of events in our TM program includes:

1. referral from the PCP to a specialist of a patient who fits the criteria for consultation, including history and physical examination, minimum required laboratory data (HCV RNA, genotype, complete metabolic panel, complete cell blood count, INR, AFP, TSH), imaging with abdominal ultrasound, liver biopsy report when appropriate, to justify consideration for treatment of chronic HCV;
2. appointment made through the TM coordinators (local community site and UC Davis Center for Health and Technology);
3. first consultation between PCP and specialist via telemedicine to discuss with the patient the severity of disease, the indications/contraindications and risks/benefits of therapy, risk of transmission counseling, and future monitoring;
4. follow ups after initiation of therapy via TM at defined intervals to review efficacy, side effects, and duration of therapy; and
5. additional visits scheduled as needed.

The PCPs also had access to a specialist on a 24/7 basis via cell phone, emails, and fax as needed. Data were collected by use of computerized or hard-copy flow charts at baseline and at standard intervals for response and safety data and dose adjustments, throughout the duration of therapy and 6 months of follow up. Medication regimens were recommended by the specialist, ordered by the PCP, and TM local pharmacies were used to dispense the drugs. After patient education, a decision was made by the PCP regarding the need for initial direct observed therapy, and more frequent follow ups, especially at the beginning of therapy, in order to maximize adherence and compliance with therapy.

Outcomes

Our primary endpoint in this study was SVR, defined as an undetectable HCV RNA level 24 weeks after completion of therapy. We also collected data on completion of therapy, reasons for early termination of therapy, and incidence and types of side effects experienced by patients, to be included as secondary outcomes.

We collected data on each patient that enabled us to determine treatment response and to monitor side effects, which included anemia, thrombocytopenia, leukopenia, weight loss, rash, fatigue, GI upset, insomnia, and depression. This data were coded by use of a standard coding system and entered into a standard database.

This patient database was encrypted with a password, and was accessible only to approved research project members for data entry.

Power Analysis

We considered whether a patient had an SVR for 48 weeks after completing therapy, measured at 24 weeks post-follow-up via PCR, as the primary endpoint (outcome), which is a binary outcome (response) variable. Let π_1 and π_2 be SVR achieved among the traditional office visit group and the telemedicine group, respectively. We wished to test the null hypothesis of no difference in SVR achieved between the two groups, i.e., $\pi_1 = \pi_2$ (OR 1), versus the alternative hypothesis that there is a difference in SVR achieved between the two groups, i.e., $\pi_1 \neq \pi_2$ (OR ≠ 1). We enrolled a total of 80 patients (40 patients in each group) for this study. The 80 patients provide power of 80 % to detect a difference of 33.1 % (π_1 = 61 %, π_2 = 27.9 %; 4.042 in terms of OR) in SVR achieved in the two groups by using the two-sided Fisher exact test at a significance level of 5 %.

Statistical Analysis

The two-sided Wilcoxon rank-sum test was used to compare the variables age, BMI, and HCV RNA level between the two treatment groups, TM and HC. The two-sided Fisher exact test was used to examine the association between treatment and each of the variables gender, ethnicity/race, HCV genotype, stage of fibrosis (metavir), SVR, completion of treatment, neutropenia, GI side effect, fatigue, depression, weight loss, insomnia, skin rash, and anemia. All analysis was performed with SAS v9.2. A p value <0.05 was considered statistically significant.

Results

At baseline, patients in both groups had similar characteristics: median age, gender, ethnicity, median BMI, median HCV RNA levels, HCV genotype, stage of fibrosis, and clinical cirrhosis were not statistically significantly different (Table 1). Because age, BMI, and HCV RNA level were not normally distributed in our sample, we used a nonparametric test, the Wilcoxon rank-sum test, to compare the median values of these variables.

The median age of patients in the TM group was 51 years compared with 53.5 years in the HC group (p = 0.65). In the TM group 53.5 % of patients were male compared with 45 % in the HC group (p = 0.06). Both groups were predominantly Caucasian (74 vs. 71 %) with adequate representation of African American (10 vs. 6 %) and Latino patients (5 vs. 15 %). Overall, patients had equivalent BMIs at initiation of therapy, with median BMI of 26.6 in the TM group and 27.6 in the HC group (p = 0.96).

Initial median HCV RNA levels in both groups approximated one million (TM: 1.2 M vs. HC: 0.9 M; p = 0.21). Most of the patients in both groups were HCV genotype 1 (TM: G1 = 65 % vs. HC: G1 = 65 %; p = 0.63). Many patients had advanced fibrosis (metavir stage 3–4) on the basis of liver biopsy results (TM: 44 vs. HC: 51 %; p = 0.65). Clinical signs of cirrhosis were similar for both groups.

With regard to clinical outcome (Table 2), SVR was similar in both groups (TM: 55 vs. HC: 43 %; p = 0.36). A greater proportion of patients treated via telemedicine completed treatment (TM: 78 vs. HC: 53 %; p = 0.03). Despite a similar number of weeks of therapy

for the two groups (TM: 36.7 vs. HC: 30.2; $p = 0.07$), TM patients had almost 10 times more face-to-face visits than HC patients (TM: 19.6 vs. HC: 2.2, $p < 0.0001$).

Overall, the side effect profiles were similar for both groups. Incidence of neutropenia, GI side effects, fatigue, depression, weight loss, insomnia, and skin rash were not significantly different. Incidence of anemia was, however, significantly higher for patients seen at UC Davis (53 %) than for those in the TM group (25 %; $p = 0.02$). The ribavirin average baseline dose was higher in the TM group than in the HC group (1,245 ± 28 vs. 1,097 ± 34, $p = 0.001$). Four patients in the TM group discontinued therapy because of depression compared with one in the HC group, and more patients in the TM group were on antidepressant medications than in the HC group (14 vs. 7).

Significantly more patients in the UCD HC group discontinued therapy because of adverse events. The main reasons for discontinuation of therapy in the UCD HC group were severe anemia, skin rash, and weight loss (Fig. 2). More patients in the TM group stopped therapy early because of severe depression; however, this was not statistically significant.

Discussion

In this research project we demonstrated that TM consultation can provide patients in remote and under-served areas with increased access to medical specialists with no drop in the level of care. TM in our current study was an effective tool for identifying and treating patients with HCV who lived in rural communities and who may otherwise have gone untreated or failed to be listed for liver transplantation.

In this small retrospective study, HCV patients treated via TM had equivalent response to therapy, achieved superior completion of therapy, and had similar overall side-effect profiles compared with a UCD HC group of HCV patients treated by means of face-to-face hepatology office visits. The superior completion of therapy is potentially related to wider utilization of directly observed therapy at the TM sites, where patients are encouraged to stay on therapy during almost weekly follow-ups. During these frequent visits, the PCP has a chance to check side effects, ensure adherence, provide psychological support, and treat adverse events more closely. TM consultation during the treatment period is usually requested on demand if any problem arises in which the PCP needs help in management.

We cannot fully explain why discontinuation was greater for patients in HC than for TM patients. Although higher doses of ribavirin were given at baseline to TM patients, it is possible anemia may have been detected earlier in TM patients as a result of closer follow up, and dose reduction of ribavirin may have prevented treatment discontinuation. The increased number of visits and direct observed therapy in the TM group may also explain why discontinuation for skin rash was numerically lower compared with HC. However, the sample size does not enable us to draw final conclusions to explain all of the differences observed.

Our model of TM consultation involves a ‘‘triangle’’ (Fig. 1) of real-time direct consultation with the patient and the PCP in the same room in the presence of the video conference specialist. Our model differs from the ECHO model that provides PCPs with HCV treatment

training via televideoconferencing and does not involve the patient in a therapeutic interaction [17]. Our method enables simultaneous communication among the three different parties: two providers and the patient.

This model also allows patients to witness direct, transparent, collegial, and educative communications between providers and allows patients to ask questions and raise concerns with both their PCPs and specialist simultaneously. Ratings of this experience on published surveys have been highly satisfactory [18]. It also enables both providers to bill for their services, because the PCP contributes to the physical examination and chart review in the presence of the patient and the specialist provides direct consultation.

Currently our model is moving toward individual contract agreements with individual institutions that have telemedicine capability to provide per hour compensation to the specialist. A specific number of hours per month are established with flexibility according to the clinical needs of the individual telemedicine site. This motivates the telemedicine site to optimize the schedule of contracted hours to maximize efficacy and minimize the incidence of ‘‘no show’’. It also motivates the specialist by financially incentivizing hours spent in Telemedicine as opposed to better reimbursed services, for example endoscopy.

Limitations of this study include the study design as a non-randomized, retrospective cohort study. It was a pilot study with a small sample size (80) and small number of telemedicine sites (5). There was limited power to detect minute differences in the primary endpoint. In addition, only one academic center was included as a comparison site and only one specialist was selected as a control for identifying differences in patient satisfaction between treatment modalities and to eliminate possible confounding by varying patient satisfaction with different providers. Patient satisfaction data have yet to be collected and analyzed.

Despite the limitations of our study, our preliminary research supports the assertion that telemedicine can potentially close the gap of access to specialty care in remote areas without sacrificing patient care quality, and can provide clinical decision-making support to PCPs with regard to best-practice treatment strategies for managing the complexities of chronic HCV infection. Furthermore, our study validates the Arora assertion that patients in remote and under-served areas with such chronic diseases as HCV infection can be effectively treated without leaving their local communities or providers.

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Conflict of interest LR receives research grant support from AbbVie, Bristol-Myers Squibb, Genentech, Gilead, Merck, Novartis, Roche, and Vertex: he is also part of the speaker bureau and advisory board for AbbVie, Genentech, Gilead, Merck, and Vertex.

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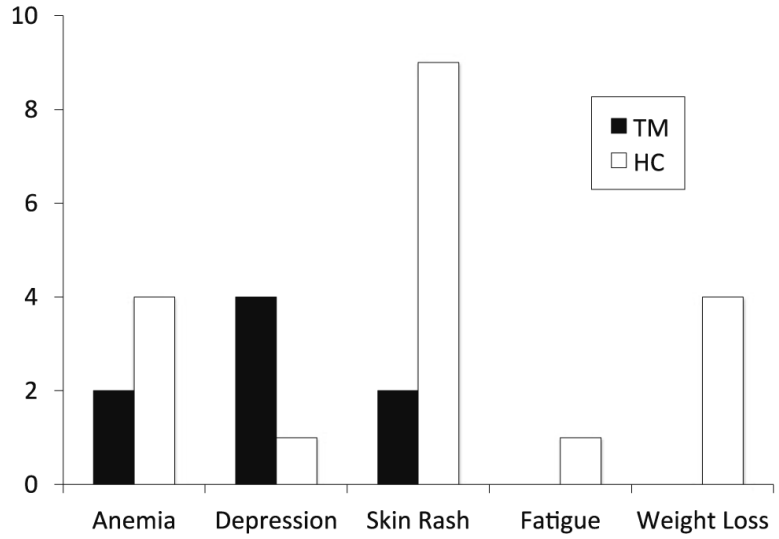

Fig. 1.

Discontinuation of therapy because of adverse events. No patients died during the course of their treatment

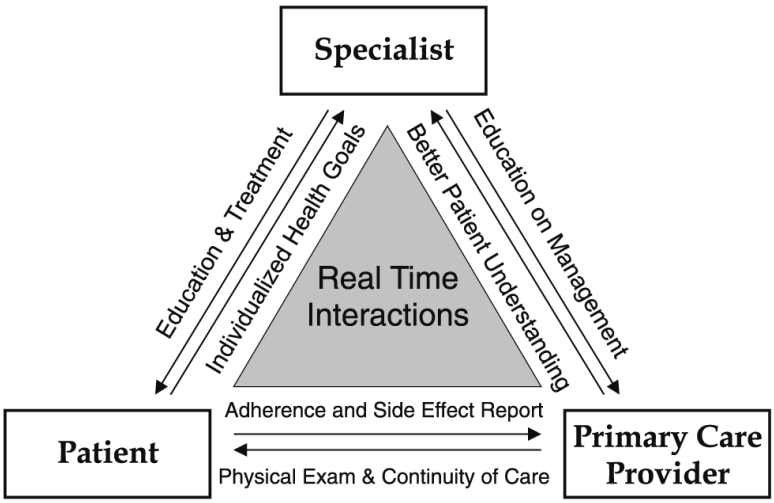

Fig. 2.

Telemedicine triad: patient, PCP, and specialist with multi-directional interactions in real time, providing care and education [19]

Table 1

Baseline characteristics for HCV patients

	TM sites (*n* = 40)	**HC (*n* = 40)**	***p* value**
Male	19	22	0.65
Female	21	18	
Age in years	51	53.5	0.06
Ethnicity			0.71
Caucasian	29	24	
Latino	2	7	
African American	4	2	
Asian	1	1	
Other	3	2	
BMI	26.6	27.6	0.96
Genotype			0.63
1	26	26	
2	6	4	
3	7	10	
4	0	0	
6	1	0	
HCV RNA level	1.2 M	0.9 M	0.21
Stage of fibrosis (Metavir)			0.65
0–2	22	18	
3–4	17	19	
Cirrhosis	11	18	0.11

Table 2

Cure success, completion of therapy, weeks of therapy, and number of face-to-face visits

	TM sites (*n* = 40)	**HC (*n* = 40)**	***p* value**
Sustained virological response (SVR)	21 (55 %)	16 (43 %)	0.36
Completion of therapy	31 (78 %)	21 (53 %)	0.03
Mean number of weeks of therapy	36.7	30.2	0.07
Mean number of face-to-face visits	19.6	2.2	<0.0001
Mean number of face-to-face visits per week of therapy	0.61	0.07	<0.001

Data on SVR available for 38 TM patients and 37 UCD patients