Hepatitis C treatment and SVR: the gap between clinical trials and real-world treatment aspirations

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Objective: Despite the remarkable improvements in pharmacologic treatment efficacy for hepatitis C (HCV) reported in published clinical trials, published research suggests that, in "real-world" patient care, these medical outcomes may be difficult to achieve. This review was undertaken to summarize recent experience in the treatment of HCV in clinical settings, examining the course of patients through the stages of treatment and barriers to treatment encountered.

Method: A comprehensive and representative review of the relevant literature was undertaken to examine HCV treatment experience outside of clinical trials in the last decade. This review found 25 unique studies with data on course of treatment and/or barriers to treatment in samples of patients with HCV not preselected for inclusion in clinical trials.

Results: Results were examined separately for samples selected for HCV infection versus HCV/HIV coinfection. Only 19% of HCV-selected and 16% of HCV/HIV-coinfection selected patients were considered treatment eligible and advanced to treatment; even fewer completed treatment (13% and 11%, respectively) or achieved sustained virologic response (3% and 6%, respectively). Psychiatric and medical ineligibilities were the primary treatment barriers.

Conclusion: Only by systematically observing and addressing potentially solvable medical and psychosocial barriers to treatment will more patients be enrolled in and complete HCV therapy.

1. Introduction

The last two decades have witnessed dramatic improvements in the treatment of hepatitis C (HCV). Sustained virologic response (SVR) has been documented in about 50% of patients using combination therapy with pegylated interferon and ribavirin, compared to previous rates of 17% with standard interferon alone [38]. Protease inhibitors alone are expected to revolutionize HCV treatment with even better treatment outcomes [20].

Despite such remarkable improvements in treatment efficacy, however, in "real-world" settings of patient care outside of clinical trials, the medical outcomes demonstrated in clinical trials may not be realized. In clinical settings, patients with HCV encounter medical and psychosocial barriers preventing them from receiving and completing the antiviral treatment needed to achieve SVR [31]. Insufficient patient readiness for treatment has been identified as a significant barrier to treatment engagement and completion. A review of the course of treatment and associated barriers to care is needed to inform effective service delivery to this challenging population.
Table 1
Articles included in the review and summary of methods in the studies represented

HCV samples (17 studies)

<table>
<thead>
<tr>
<th>Authors/year</th>
<th>Sample</th>
<th>N</th>
<th>Data collection method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bini et al., 2005</td>
<td>Convenience sample of patients with HCV from 24 VA medical centers</td>
<td>4048</td>
<td>Systematic interviews of patients and interviews of their treating clinicians about their opinions of these patients’ suitability for treatment (compared with standardized criteria for treatment eligibility)</td>
</tr>
<tr>
<td>Butt et al., 2005</td>
<td>Military veterans with HCV referred to a GI/hepatology specialty clinic</td>
<td>354</td>
<td>Prospective data from medical record review</td>
</tr>
<tr>
<td>Cawthorne et al., 2002</td>
<td>Patients with HCV referred to a VA HCV clinic</td>
<td>557</td>
<td>Chart review</td>
</tr>
<tr>
<td>Delwaide et al., 2005</td>
<td>Patients with HCV in a community liver clinic</td>
<td>299</td>
<td>Retrospective chart review clinical assessments by patients’ treating hepatologist</td>
</tr>
<tr>
<td>Doab et al., 2005</td>
<td>Convenience sample of intravenous drug users with HCV from primary health or methadone clinics in Sydney</td>
<td>100</td>
<td>Interviewer-administered surveys</td>
</tr>
<tr>
<td>Falck-Ytter et al., 2002</td>
<td>Patients with HCV at teaching county hospital liver clinic</td>
<td>293</td>
<td>Medical record review</td>
</tr>
<tr>
<td>Grebely et al., 2008</td>
<td>Convenience sample of patients with HCV from two inner-city multidisciplinary community clinics in Canada</td>
<td>188</td>
<td>Self-administered questionnaires</td>
</tr>
<tr>
<td>Groom et al., 2008</td>
<td>Military veterans with HCV</td>
<td>520</td>
<td>Medical record review</td>
</tr>
<tr>
<td>McNally et al., 2006</td>
<td>Convenience sample of patients with HCV from various healthcare clinics (5 large hospitals, needle exchange sites, Hepatitis Council of Victoria and community health centers) and nonclinical sites (news media) in the state of Victoria, Australia</td>
<td>224</td>
<td>Prospectively administered 78-item patient questionnaire</td>
</tr>
<tr>
<td>Mehta et al., 2008</td>
<td>Intravenous drug users with HCV treated at Johns Hopkins Hospital clinics</td>
<td>597</td>
<td>Longitudinal cohort study using prospective administration of a patient questionnaire</td>
</tr>
<tr>
<td>Morrill et al., 2005</td>
<td>Patients with HCV from an outpatient liver clinic</td>
<td>1317</td>
<td>Electronic medical record review and individual interviews with patients’ primary care providers</td>
</tr>
<tr>
<td>Muir et al., 2002</td>
<td>Consecutive sample of patients with HCV at Durham VA Medical Center</td>
<td>100</td>
<td>Information was gathered prospectively on demographics, medical history, current medical condition, psychiatric history and psychiatric status assessments</td>
</tr>
<tr>
<td>Rowan et al., 2004</td>
<td>Consecutive sample of patients with HCV from 5 large hospitals, needle exchange sites, Hepatitis Council of Victoria and community health centers</td>
<td>580</td>
<td>Cross-sectional semistructured interviews</td>
</tr>
<tr>
<td>Seal et al., 2007</td>
<td>Patients with untreated HCV from gastroenterology, hepatits and infectious disease clinics at 24 VA medical centers who were followed through treatment</td>
<td>4318</td>
<td>Cross-sectional semistructured interviews</td>
</tr>
<tr>
<td>Zickmund et al., 2004</td>
<td>Patients with chronic HCV selected from hepatology clinics, with 80% full participation</td>
<td>322</td>
<td>Cross-sectional semistructured interviews</td>
</tr>
</tbody>
</table>

Coinfected (HCV+HIV) samples (8 studies)

<table>
<thead>
<tr>
<th>Authors/year</th>
<th>Sample</th>
<th>N</th>
<th>Data collection method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cacoub et al., 2006</td>
<td>HIV/HCV-coinfected patients of 71 physicians from specialized treatment centers in metropolitan France</td>
<td>380</td>
<td>Physician surveys regarding their patients</td>
</tr>
<tr>
<td>Fleming et al., 2003</td>
<td>HIV/HCV-coinfected patients from Boston Medical Center coinfection clinic</td>
<td>180</td>
<td>Prospective study through questionnaires, physical examinations and medical record review</td>
</tr>
<tr>
<td>Fleming et al., 2005</td>
<td>HIV/HCV-coinfected patients from Hepatitis &amp; AIDS Liver Outcome (HALO) study at Boston Medical Center</td>
<td>94</td>
<td>Prospective study through questionnaires, physical examinations and medical record review</td>
</tr>
<tr>
<td>Hall et al., 2004</td>
<td>HIV/HCV-coinfected patients from REACH program in San Francisco (64% participation)</td>
<td>182</td>
<td>Prospective study using questionnaires and baseline laboratory assessments</td>
</tr>
<tr>
<td>McLaren et al., 2008</td>
<td>HIV/HCV-coinfected patients at Ottawa Hospital Viral Hepatitis Clinic</td>
<td>102</td>
<td>Retrospective medical record review</td>
</tr>
<tr>
<td>Murray et al., 2011</td>
<td>HIV/HCV-coinfected patients presenting to a HCV program at a HIV clinic</td>
<td>134</td>
<td>Retrospective medical record review</td>
</tr>
<tr>
<td>Nunes et al., 2006</td>
<td>Volunteer sample of treatment-eligible HIV/HCV-coinfected patients recruited from HIV clinics (84% had complete data)</td>
<td>168</td>
<td>Interviews of patients and primary care providers and medical record review</td>
</tr>
<tr>
<td>Thompson et al., 2005</td>
<td>HIV/HCV-coinfected patients in free lunch programs, homeless shelters and single room occupancy hotels in San Francisco REACH program (86% participation) and their 52 primary care providers (84% participation)</td>
<td>133</td>
<td>Quarterly structured interviews for patients and semistructured interviews for providers</td>
</tr>
</tbody>
</table>

1.1. The Andersen health services model for review of barriers to care for HCV

The Andersen [2] model of health services provides a conceptual framework to organize the review of barriers to HCV treatment [24]. This model facilitates the identification of modifiable patient and healthcare system factors that may lead to improved coordination of care and related health outcomes [15]. Thematic categories in the Andersen model are individual/patient factors (need, enabling and predisposing factors), health service system factors (insurance
systems, qualified treatment force, fragmented specialty care, medical therapeutics) and treatment-related factors (accessibility of care, availability of service, support, affordability of care and knowledge). Modifiable factors in these categories contain items that can be targeted for interventions to improve health outcomes.

2. Methods

2.1. Selection of research articles and organization of the findings

A comprehensive and representative review of the literature on the course of HCV treatment in clinical care settings was undertaken to examine HCV treatment experience outside of clinical trials in the last decade. Articles from the last decade describing the course of treatment in HCV patient care settings were sought to investigate how patients engage in and complete HCV treatment, and the barriers to treatment and course of treatment[1]. Findings from this review were generally organized based on the Andersen model categories. This review was designed to investigate experience in the course of HCV treatment in real-world care settings in a representative core group of articles with original data related to the course of treatment and barriers to treatment of HCV encountered in samples of largely unselected patients presenting to clinical care settings. This review was not intended to include the entire collection of numerous studies utilizing selected, circumscribed samples such as patients referred for randomized controlled pharmaceutical trials and studies of patients already selected for treatment eligibility or to be exhaustive of all published studies of HCV.

For this review, a PubMed search on the phrase “course of hepatitis C treatment” yielded 2024 articles. These articles were considered, along with all the relevant studies found in references in them, for inclusion in this review. Because most articles in the search represented randomized controlled trials or were confined to patient samples previously selected for treatment, they were not included. The remaining studies provided data on the course of patient flow through HCV treatment and/or barriers to care in this progression in non-clinical-trial patient samples and were thus included in this review. This process yielded a total of 26 articles; one[7], however, had a sample that substantially overlapped with that of an earlier article by the same research group[8]. Exclusion of that article resulted in a total of 25 unique studies (17 for HCV-selected samples and 8 for HCV/HIV-coinfected samples) with nonoverlapping original data (Table 1). Two of these 25 articles[11,39] did not provide summary data on patient flow through the basic treatment progress stages, but included informative detail on categories of barriers to treatment (Table 2). Thus, 23 of the 25 articles reviewed here (15 for HCV-selected samples and 8 for HCV/HIV-coinfected samples) provided summary data on the stages of patient progress through treatment (see below). This review provides results separately for studies of non-clinical-trial samples of patients with HCV and those with HCV/HIV coinfection based on preexisting evidence of differences between these two groups in barriers to treatment and course of treatment[1].

2.2. Patient flow through stages of treatment

For each study reviewed, patient flow data were recorded as the proportions proceeding through five basic stages of treatment progression: (a) presenting for clinical care (i.e., inclusion in the sample, 100% by definition), (b) treatment eligibility, (c) starting treatment, (d) completing treatment and (e) attainment of SVR. Two independent abstracters examined articles included in this review and recorded statistics presented in each of the specified categories. Because the presentation of findings was not systematic among the studies included in this review, ambiguities in designation of
assignment to these categories were resolved by team consensus by
the members of this research team whose expertise includes
infectious disease, hepatology, psychiatry and social work.

2.3. Categories of barriers to care

Categories of barriers to treatment, informed by the Anderson
model, identified in these articles were medical ineligibility, patient-
related barriers, provider-related barriers and medical care systems
barriers. Barriers reported in these studies were tabulated for each
category of barrier for each study reviewed. Different articles grouped
and reported their findings for the types of barriers in different ways
and often included overlapping numbers in more than one category.
Because these categories were variably represented in these studies,
and often in small numbers, it is not possible to systematically
summarize the proportions of patients encountering these barriers in
tables; general observations about the representation of these barriers
in real-world HCV treatment in these studies are provided in text.

2.4. Statistical analysis

Summary statistics were developed with numbers and proportions
completing each of the five stages of the patients’ progress through
treatment. Proportions were calculated as the total number of
patients completing a stage divided by the combined number of
patients represented in the studies reporting numbers on that stage.
These statistics were recalculated separately for only the studies that
had complete data for all five stages; Figs. 1 (HCV-selected samples)
and 2 (HCV/HIV-coinfection samples) illustrate the results of both
of these calculations of proportions at each stage of treatment
progress superimposed upon one another in the same figures for
direct comparison.
3. Results

Studies in this review included samples from a variety of treatment subpopulations, including military veterans, injection drug users and HCV-infected patients with other risk factors. The original data obtained for these articles were collected from patient medical records, patient interviews or questionnaires, and physician surveys. Table 1 lists the samples studied and the research methods in these studies, separately for HCV-selected and for HCV/HIV-coinfection selected samples.

Table 2 presents data on the proportions of patients in these studies who successfully proceeded through five stages of study inclusion and treatment. Figs. 1 and 2 (for HCV-selected and for HCV/HIV-coinfection selected samples, respectively) illustrate the proportions of patients proceeding through each of these treatment stages, including separate results for all studies and for just those studies with complete data in all treatment stages. The proportions completing the stages of treatment dropped dramatically at the stage of treatment eligibility, 39%–41% for HCV-selected and 16%–18% for HCV/HIV-coinfection selected samples. Only a fraction of these patients (19%–21% of all HCV-selected and 5%–16% of all HCV/HIV-coinfection selected samples) commenced treatment, and even fewer completed treatment. Few HCV-only or coinfected HCV/HIV patients in either group (3%–4% and 1%–6%, respectively) actually achieved SVR in these studies.

The variety of reasons for lack of treatment received and proportions of each of these reasons varied from study to study. The most commonly cited categories of barriers to care in published studies were medical ineligibilities (11 studies of HCV and 7 studies of HCV/HIV coinfection) and patient barriers (13 studies of HCV and 7 studies of HCV/HIV coinfection). Less often described categories of barriers to care were care provider barriers (five studies of HCV and four studies of HCV/HIV coinfection) and system barriers (four studies of HCV and two studies of HCV/HIV coinfection).

Among the category of medical ineligibilities for treatment, the ineligibilities mentioned in most studies were substance use disorder (six HCV and six HCV/HIV-coinfection studies), psychiatric disorder (seven HCV and six HCV/HIV-coinfection studies) and medical comorbidity (eight HCV and six HCV/HIV-coinfection studies). The medical ineligibility reasons mostly commonly reported by the studies describing them were hematologic abnormalities such as severe anemia and thrombocytopenia (32% of HCV and 21% of HCV-coinfection studies), previous treatment (28% of HCV studies), and medical (34% of HCV and 25% of HCV/HIV-coinfection studies) and psychiatric (33% of HCV and 28% of HCV/HIV-coinfection studies) comorbidity. Stage of liver disease (either too advanced to tolerate treatment or too benign to warrant therapy) and HIV infection also represented additional sources of treatment eligibility for patients in some studies of both HCV-selected and HCV/HIV-coinfection samples.

The category of patient barriers included patients' attitudes, personal resources, preferences and ultimate decisions. Among the category of patient barriers to treatment, the ones mentioned in most studies were refusal of recommended treatment (eight HCV and four HCV/HIV-coinfection studies), adherence risk (seven HCV and four HCV/HIV-coinfection studies), fear of side effects (six HCV and two HCV/HIV-coinfection studies) and loss to follow-up (five HCV studies and one HCV/HIV-coinfection study). The most commonly reported patient barriers by studies reporting them were low confidence in treatment effectiveness (29% of HCV studies), perception of liver disease as too mild (25% of HCV and 4% of HCV/HIV-coinfected studies), not feeling symptoms (16% of HCV studies), and competing medical and/or psychosocial priorities (10% of HCV and 12% of HCV/HIV-coinfection studies), such as need to continue working that could be compromised by treatment, desire for pregnancy or contraception issues, desire to drink and take drugs rather than abstinence required to undergo treatment or desire to focus on HIV treatment rather than starting HCV treatment.

Care providers were reported to impose additional barriers to treatment. The most commonly mentioned care provider barriers mentioned were failure to discuss the illness with the patient and deferral of treatment (three HCV studies each). Other reported care provider barriers were failure to screen for HCV or refer to treatment, lack of knowledge or skill for diagnosis and treatment of HCV, poor communication skills and care provider stigma (e.g., related to drug use, homosexuality and sexual promiscuity).

Only six studies (four of HCV-selected samples and two of HCV/HIV-coinfected samples) presented findings related to system barriers to treatment. System barriers to treatment mentioned in these studies were general lack of knowledge about the illness (e.g., importance of screening or treatment not generally appreciated) and lack of access to care (e.g., availability and affordability).

4. Discussion

Despite recent advances in antiviral treatments for HCV, this review suggests that only a small fraction of patients with HCV receive treatment necessary to attain SVR. Confirming dismal impressions of other researchers [3,32,33] that a small proportion of patients with HCV actually receives antiviral therapy, the current comprehensive review of the course of treatment for HCV in real-world care settings demonstrated that not even 20% of patients with HCV commence treatment and even far fewer successfully complete treatment or achieve SVR. Booth [4] noted that the benefits demonstrated in clinical trials may not be realized at the population level because patients, physicians and health care in the general population may differ from the controlled contexts of clinical trials.

New and emerging directly acting antivirals, used in conjunction with pegylated interferon and ribavirin, are highly effective treatments to cure HCV. However, the cost of these medications will be far higher than for interferon and ribavirin alone, and the side effects are expected to be even more substantial with the addition of directly acting antivirals. Therefore, it is critical to address patient barriers to treatment so that the benefits of emerging scientific achievements can be realized in the care of HCV in the community.

The current review found medical and psychosocial problems to be the major impediments to treatment, especially substance use disorder, psychiatric disorder and medical comorbidity, in rates of one fourth to one third or even more. Thus, more patients could be treated, especially in the coinfected groups, if these barriers or obstacles were resolved. Management of these problems in patients with psychiatric and/or substance use problems has the potential to improve their treatment readiness and likelihood of successfully completing HCV treatment [34–36]. It is imperative that HCV treatment programs have psychiatric resources available to them. The use of antidepressants prior to or during active HCV treatment could do much to improve the proportion of patients achieving SVR, especially for patients on interferon-based therapies. New antivirals for HCV treatment, some which are potent CYP3a inhibitors, will need the expertise of a psychiatrist who can select appropriate psychiatric medications to avoid detrimental drug-drug interactions.

HCV patients also have other social barriers to treatment. Some may lack adequate housing, social support, transportation to treatment and needed information about HCV. Many of these social barriers are complex and will demand a multidisciplinary approach for their resolution. Psychologists and social workers may need to provide individual psychotherapy or support groups for patient/family members. Physician assistants and advanced practice nurses who specialize in HCV care can provide pretreatment education and consultation throughout the treatment period. The use of these midlevel providers can do much to coordinate these needed resources. Although HCV treatment is rapidly changing and the future holds promise of effective, well-tolerated oral therapy, HCV treatment...
will continue to require multidisciplinary care to address the comprehensive impact of this disease on the lives of these patients. Can efforts and resources be brought to bear on these problems so that these barriers to treatment can find resolution? Unfortunately, not all the barriers can be removed, and some patients have medical comorbidities that make treatment impossible. There will probably always remain subgroups of patients for whom efforts to move them to treatment may not be appropriate, such as patients of advanced age or minimal level of disease. Even if clinical trials could achieve 100% efficacy, given the current situation, the patients who complete treatment and achieve SVR represent only a small fraction of the total universe of HCV-infected patients. As explicated by Booth [4], it cannot be assumed that findings from landmark studies will substantially benefit patient care in “real-world” settings without studies to examine outcomes in more general patient populations.

This review was limited to studies of non-clinical-trial samples of patients found in a variety of clinical settings selected for HCV infection or HCV/HIV coinfection. Clinical trials were excluded from this review because of restrictions or exclusion criteria that precluded examination of the natural course of disease in more general HCV patient populations. Although this literature review was not intended to be exhaustive, it identified a core group of articles with data on the course of HCV treatment in patient populations in “real-world” patient care settings. The consistency of the findings (i.e., the circumscribed range of rates all below one half for starting treatment, below one third for completing treatment and below one fourth for attaining SVR, without outliers among the 25 studies providing summary data in these categories) argues compellingly for the representativeness of the articles reviewed and the validity of the findings.

This review was further limited by the available literature that was often inconsistent in focus and organization. To organize this review, therefore, it was necessary to identify consistent themes and develop conventions for categorization of the content provided. A methodological strength was the independent review of the studies by separate raters and the multidisciplinary representation of the researchers who collaborated on the review and resolved potential discrepancies in categorizing the findings. The categories in the review of barriers to care were limited by the presentation of the findings in the individual studies, sometimes overlapping categories and insufficient representation within studies to produce systematic summary statistics.

The findings of this review suggest that many of the barriers to care evidenced in this literature can be readily addressed through education (particularly at the system level and at the patient level) or by treating a comorbid condition prior to, or in concert with, receiving HCV treatment. This review has illuminated areas where efforts could be focused in current care that may have the potential for large payoff in terms of helping patients become more eligible for treatment. The findings also indicate the need for development of new interventions to help patients engage in treatment and achieve success in completing treatment.

In France, Cabouc and colleagues [6] noted recent substantial increases in the proportions of patients with HCV who received treatment, and these yielded improved SVR rates. The main forces behind the increase in treatment rates were that treatment was considered less questionable and the increasing use of noninvasive liver damage tests reduced the barrier historically presented by reliance on liver biopsies. Cabouc and colleagues [7] remarked, “It is striking to note that most of the reasons [for non-treatment] which decreased were related to physician assessment or a priori.” This group’s work identified the potential for increasing treatment effectiveness through targeting specific barriers to treatment. The current review identified several barriers to care needing further attention to enable successful treatment of higher proportions of these patients.

The findings of this review may be generalizable to other areas of medicine where access to potentially effective treatment is limited. Identification of potentially modifiable barriers to care for general medical conditions and development of novel solutions could significantly increase treatment effectiveness in medical care.

References

[7] Cabouc P, Halff P, Rosenthal E, et al. Treatment of hepatitis C virus in human immunodeficiency virus-infected patients in “real-world” settings without studies to examine outcomes in more general patient populations. This review was limited to studies of non-clinical- trial samples of patients found in a variety of clinical settings selected for HCV infection or HCV/HIV coinfection. Clinical trials were excluded from this review because of restrictions or exclusion criteria that precluded examination of the natural course of disease in more general HCV patient populations. Although this literature review was not intended to be exhaustive, it identified a core group of articles with data on the course of HCV treatment in patient populations in “real-world” patient care settings. The consistency of the findings (i.e., the circumscribed range of rates all below one half for starting treatment, below one third for completing treatment and below one fourth for attaining SVR, without outliers among the 25 studies providing summary data in these categories) argues compellingly for the representativeness of the articles reviewed and the validity of the findings.

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