Review Article

Predictors of Non-Adherence of Hepatitis C Patients to Treatment: A Systematic Review

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ABSTRACT

Background: Predictors of non-adherence to treatment of the hepatitis C patients are complex and unclear. So far, there are limited studies that addressed these predictors.
Objective: To identify the common predictors of non-adherence to treatment among hepatitis C patients.
Methods: The authors reviewed literature on predictors or factors associated with non-adherence to treatment of hepatitis C patients that was published from 2007 to 2017 in PubMed, Proquest, Science Direct, Wiley, SAGE, and Ebscohost. The retrieved articles were subjected to inclusion criteria as follows: patients aged ≥ 18 years with chronic hepatitis C, patients treated with Pegylated interferon and Ribavirin, full text articles, quantitative designs, and the English language. All articles involving clinical trials were excluded from review.
Results: Six studies were included in this review; five cohort studies and one cross-sectional study. Populations of these studies ranged from 72 to 5,760 individuals. According to STROBE checklist, representativeness of study sample and consideration of confounders were insufficient in most studies. Additionally, not all studies addressed potential sources of bias and applied adjusted analysis for confounders. Most studies examined condition-related factors that had negative effect on adherence to treatment like depression, psychiatric disorders and anemia. Another group of factors, i.e., patient-related factors, social and economic factors, therapy-related factors, and health care system-related factors were examined only by one study or two studies.
Conclusion: Many factors have an influence on adherence and handling these factors, particularly in clinical sites, is very important for achievement of good adherence to hepatitis C treatment.

*Keyword*s: predictors, factors, non-adherence to treatment, hepatitis C patients

INTRODUCTION

Hepatitis C virus (HCV) is a common health threat that causes liver disease. In 2015, it was estimated that 71 million people had chronic HCV infection worldwide. According to the records of the World Health Organization (WHO), the regions most affected by the HCV are the Eastern Mediterranean region, with a prevalence of 2.3%, and Europe, with prevalence of 1.5%. [1] In other WHO regions, the prevalence of HCV infection varies from 0.5% to 1.0 %.In 2015, mortality because of viral hepatitis was due to chronic liver disease where about 720,000 people died because of cirrhosis and 470,000 died owing to hepatocellular carcinoma. [1]

The main aim of hepatitis C therapy is to cure the infection. A sustained

virological response (SVR), which is equivalent to virological cure, is defined as undetectable HCV RNA 12 weeks or 24 weeks after treatment completion. Nearly 99% of the patients with chronic hepatitis C (CHC) are cured from infection when they achieve SVR, which is mostly realized in patients without cirrhosis associated with resolution of liver disease, while patients with cirrhosis remain at risk of serious complications. [2]

Until 2011, the combination of Peg IFN and RBV treatment for 24 or 48 weeks was an approved standard treatment for chronic hepatitis C. However, new medicines and new combinations of treatments became available in the USA and the EU in the years 2011, 2014, and 2015. Though, these new medications are still expensive and not used in all countries all over the world. [3] As expected, the advances in treatment regimens of the hepatitis C infection will reduce the HCV-related morbidity and mortality. [3]

Adherence to medication is defined as the proportion of prescribed doses of medication actually taken by a patient over a specified period of time, or the extent to which patients take medications as prescribed by their health care providers. Adherence can be measured by several methods, including patients' self-reports, pill counts, prescription refill rates, electronic medication monitors, and measurement of drug level in the blood. [4] However, there is no golden standard for measurement of adherence among the hepatitis C patients. In other respects, all adherence measurements have limitations.

According to WHO, [5] adherence to treatment is a multidimensional phenomenon controlled by the interplay of five sets of factors: (i) economic and social factors, (ii) health care team and system-related factors, (iii) condition-related factors,(iv) therapy-related factors, and (v) patient-related factors. [5]

There are few systematic review studies that addressed predictors or factors that can affect adherence of the hepatitis C

patient to treatment. Matheset et al. [6] reported that psychiatric disorders and high doses of RBV had a negative effect on adherence. However, the HIV coinfection and the hemoglobin level are associated with a positive effect on adherence. Lieveld et al. [7] investigated adherence to treatment of hepatitis C and hepatitis B patients and found that psychiatric disorder, illicit drug use, and HIV coinfection were the most common predictors of adherence of those patients to treatment.

In the present systematic review, the author analyzed some of the studies which reported predictors of non-adherence to treatment. The research question was: What are the predictors of non-adherence of the hepatitis C patients to treatment?

METHODS

Six electronic databases were searched to find information: Ebscohost, Proquest, PubMed, SAGE, Science Direct, and Wiley. These databases were searched for articles published from 2007 to 2017. In addition, Google Scholar was screened to find any relevant studies. The key search terms used were: i) predictors or factors, ii) affecting or stimulating or influencing, iii) treatment adherence or medication adherence, and iv) hepatitis C patients.

The retrieved articles were initially screened based on titles and abstracts to exclude irrelevant articles. Then, the retrieved articles were screened based on the inclusion and exclusion criteria. Afterwards, the full text of each seemingly relevant article was revised carefully to decide on whether to include the article in, or exclude it from, the review. In addition, the lists of references of all selected articles were screened for potentially relevant articles. The inclusion criteria were: i) Patients with hepatitis C who are ≥18 years old, ii) predictors or factors affecting adherence, iii) patients treated with PegIFN and RBV, iv) full text articles, v) studies with quantitative designs, and vi) manuscript language is the English language. Studies not meeting the foregoing criteria, as well as studies

involving clinical or drug trials, were excluded.

Assessment of the quality of the selected studies

The STROBE statement or check list (STrengthening the Reporting of OBservational studies in Epidemiology) was used to assess the quality of the studies selected for review. This checklist was originally developed by international collaboration of statisticians, epidemiologists, and journal editors. [8] The STROBE checklist provides a useful list of the important criteria needed to evaluate studies, though it is not tool for evaluation of quality of the primary studies. This checklist consists of 22 items that are considered essential for good reporting of observational studies. It comprises i) title and abstract, ii) introduction, iii) methods, iv) participants, v) results, vi) discussion, and vii) other information such as funding. This checklist is very helpful, especially for researcher who have limited experience with observational studies and who did never receive training on epidemiology. [8]

Information was extracted from the selected studies about the authors, year of publication, country where the studies were conducted, research design, sample size, and the main findings.

RESULTS

Three hundred forty six potentially relevant articles were identified. After revising the titles and the abstracts or full texts of the articles, only seven studies fulfilled the inclusion criteria. Figure 1 summarizes the whole search process.
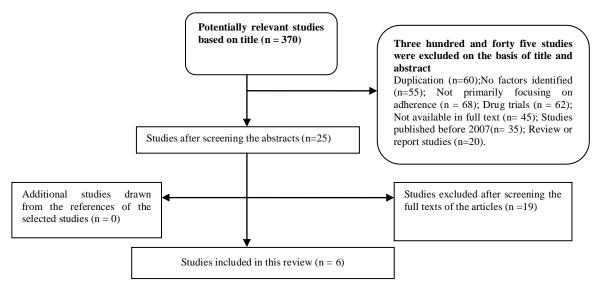

Figure 1. Summary of the literature search process

Results of assessment of the quality of the studies included in this review based on the STROBE checklist are presented in Table 1.

The main information of interest to this study about the included studies was extracted and summarized in Table 2.

Table 1: Assessment of the quality of the studies included in this review based on the STROBE checklist

Study	Scores on the STROBE checklist*	Total Score
	1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22	
Evon et al. (2013) [9]	+ + + + + + + + + - + + + + + + - + + + + +	20/22
Ravi et al. (2013) [10]	- + + + + + ++ + - + + + + + - + + + + +	19/22
Re III et al. (2011) [11]	+ + + + + + + + + + + + + + + + - - + + - + +	19/22
Wagner et al. (2011) [12]	+ + + + + + + + - - + + + + + + - - + + + - +	17/22
Tanioka et al. (2009) [13]	+ + + + + + + + - - - + - + + + + - + + + - -	16/22
Martin-Santos et al. (2008)) [14]	+ + + + + + + + + + - - + + + + + - + + - + +	18/22

(+) the criterion was clearly satisfied; (–) the criterion was not clearly satisfied
*The total score is determined by counting the number of criteria that are satisfied

Table 2: The main characteristics of the studies included in the current review

Author(s), year of publication, and study location	Study design	Sample size	Adherence measurement tools	Adherence rate	Main findings
Evon et al. (2013) [9] United States	Cohort study	401	Medication Event Management System (MEMS)	Adherence to PegIFN during the first 24 weeks was 90.2% and in week 48it was 94.5%. Adherence to RBV in the 24th week was 85% and in the 48th week it was 75%.	Predictors of non-adherence from baseline to 24 weeks were younger age, lower education, being unmarried, public or no insurance, or worse baseline headaches. Higher baseline depression predicted missing PegIFN from 24 to 48 weeks, and patients without employment or private insurance were more likely to miss RBV within 24 to 48 weeks.
Ravi et al. (2013) [10] Iran	Cohort study	190	Self-report and pill counting	Ranges of percentages of adherence to PegIFN, RBV, and a combination of them over the first 24 weeks of therapy were 35.4-65.8%, 46.3-56.8%, and 28.4-51.1%, respectively.	Delay in receiving new prescription and adverse drug reactions were reported for patients as the most common cause of non-adherence.
Re III et al. (2011) [11] United States	Cohort study	5,706	Pharmacy refill data	Adherence to PegIFN during 24 weeks was 95.4% while adherence to RBV was 86.1%. Adherence after 48 weeks was 89.3% for PegIFN and 76.1% for RBV.	Patients having leukopenia or anemia and prescribed growth factors as well as patients having thyroid dysfunction and prescribed thyroid hormone replacement had slightly higher mean adherence to PegIFN and RBV.
Wagner et al. (2011) [12] United States	Cross-sectional study	72	Single visual analog scales	Percentages of adherence to PegIFN and RBV treatments over the entire period were 93.8% and 72%, respectively.	The patients who had low adherence were more likely to have active psychiatric diagnosis at the time of treatment start than patients with good adherence (67% vs. 38%); no other variables were significantly associated with adherence to the HCV treatment.
Tanioka et al. (2009) [13] Japan	Cohort study	363	Not reported	An 80% adherence was more frequent in the re-treatment (62%) than in the naïve group (46%) in centers with more patients treated (57%) than in those with less patients treated (46%).	Re-treatment patients, center with more patients treated, patient age (< 55 years), male, genotype 2, and dosage of interferon per weight (< 0.13 million units/kg) were associated with achievement of 80% adherence to combination therapy.
Marti`n-Santos et al. (2008) [14] Spain	Cohort study	176	Not reported	One hundred and twenty seven (87%) of 146 patients with good adherence at baseline without incidence of depression or anxiety disorders. During therapy, the percentage of patients with good adherence was lower in those with depression and/or anxiety (79% vs. 91%).	Higher risk for psychiatric disorders during PegIFN and RBV therapy was found in patients with baseline high depression score, history of a depressive disorder or alcohol dependence, and genotype other than 1.

All of the studies were quantitative in nature (five cohort studies and one cross sectional study). The populations of these six studies ranged from 72 to 5,760 individuals. According to STROBE checklist, the representativeness of the study sample and the consideration of confounders were insufficient in most studies, and not all studies addressed the potential sources of bias and, consequently, they did not apply an adjusted analysis for confounders.

Predictors of non-adherence identified by the reviewed previous studies

This review categorizes the predictors of non-adherence of the hepatitis C patients to treatment into five groups of factors.[5] A discussion of the factors in each of these five groups follows.

1. Economic and social factors

The most common economic and social factors that have a significant influence on adherence, especially in developing countries, are poverty, low socio-economic status, low level of education, illiteracy, lack of effective social

support, unemployment, distance from the treatment centers, unstable living conditions, high treatment costs, high transportation costs, family dysfunction, culture and the beliefs about the disease and treatment. [5] Two studies have data on this group of factors. One of them is the cohort study of Evon et al. [9] This study reported that low education, unemployment, being unmarried, and public or no insurance have negative effects on adherence to treatment with both PegIFN and RBV, and that patients without private insurance or employment were more likely to miss RBV from weeks 24–48. The second study is the cohort study of Ravi et al. (2013), [10] which found that the financial issues were the main reason for non-adherence to both PegIFN and RBV treatments for18.4% of the patients. Other less common factors were unavailability of drug and traveling.

2. Patient-related factors

The patient-related factors for non-adherence to treatment are represented by the knowledge, resources, beliefs, attitudes, and the perceptions and the expectations of the patients. As well, these factors include psychosocial stress; forgetfulness; low motivation; anxiety about potential adverse effects; lack of a perception of the need for treatment; insufficient knowledge about, and skill in, managing the disease symptoms and the treatment; lack of perception of the effect of treatment; and negative beliefs about efficacy of the treatment. [5] Studies supporting these factors include the study of Evon et al. [9] who stated that being African American of younger age has negative effect on adherence to treatment and that a high baseline depression predicted missing PegIFN from weeks 24–48. These researchers also reported several common reasons for missed doses, including feeling good; change in daily routine; feeling sick or ill; and simply forgetting. Ravi et al. [10] reported that feeding up with drugs, feeling ill, and being forgetful were less common reasons for non-adherence to both the PegIFN and RBV. Tanioka et al. [13] stated

that an adherence percentage of 80% was more frequent in the younger male patients than in the re-treatment patients (62%) and the naïve patients (46%).

3. Condition-related factors

The condition-related factors include specific illness-related stresses challenged by the patient, especially those linked to the severity of the symptoms; the level of the psychological, physical, vocational, or social disability; the severity of the disease; the rate of progression; and the accessibility to effective treatment. Comorbidities, such as depression, are an important predictor of the adherence behavior in the CHC patients. [5] Almost all the studies included in the present review reported on this group of factors. For example, Evon et al. reported that a high baseline depression predicted missing PegIFN from weeks 24–48, and Re et al. [9] found that patients who had leukopenia or anaemia and prescribed growth factors as well as patients who had thyroid dysfunction and prescribed thyroid hormone replacement had slightly higher mean adherence to PegIFN and RBV than other patients. In addition, patients using methadone exhibited reduced adherence.

Wagner et al. [12] found that the patients who had low adherence were significantly more likely to have active psychiatric diagnosis at the time of treatment initiation than the patients with good adherence (67% vs. 38%, *p*<.05). Marti`n-Santos et al. [14] reported that a higher risk for psychiatric disorders during PegIFN and RBV therapy was found in patients with a high baseline depression score (27.8 odds ratio of 95% CI (2.82-333.0)). During therapy, patients without incidence of depression or anxiety disorders had good adherence (91.0%) compared to patients with good adherence who had incidence of depression or anxiety disorders (79.0%).

4. Therapy-related factors

There are numerous therapy-related predictors that affect adherence. Most

prominent are the predictors related to the complexity of the medical regimen, duration of treatment, previous treatment failures, frequent changes in treatment, immediacy of beneficial effects, side-effects, and the availability of medical support for dealing with them. Adherence interventions should be tailored to the needs of the patient in order to achieve the maximum impact. [5] Some of the reviewed studies have data on this group of factors. For instance, Ravi et al. [10] studied the factors which can be the reason for non-adherence to both the PegIFN and RBV treatments. Drug side effects were responsible for 14.7% of the non-adherence to PegIFN treatment and 19.2%of the non-adherence to the RBV treatment. Less common factors like unavailability of drug and drug loss (spill) during preparation for injection were also identified.

5. Health care team and system-related factors

The health care team and system-related factors include many factors that have negative impacts on adherence. These include inadequately-developed health services with insufficient or non-existent compensation by health insurance plans, absence of relevant knowledge among the health care providers, lack of training on managing chronic diseases, overworked health care providers, lack of feedback on performance, lack of knowledge about adherence to treatment and about effective interventions for its improvement, lack of rewards, poor capacity of the system for educating the patients and providing follow-up, and short consultations. [5] Ravi et al. [10] reported delay in receiving prescription as the most common cause of non-adherence to the PegIFN α (31.62%) and RBV (20%) treatments. Furthermore, Tanioka et al. [13] stated that 80% adherence to both the PegIFN and RBV treatments was more frequent in centers with more patients treated (57%) than in those with less patients treated (46%). They also indicated that the patient's motivation and the

physician's treatment experience may be important for a better adherence to a combination therapy by the patients with chronic hepatitis.

DISCUSSION

There are many factors that affect adherence of the hepatitis C patients to treatment. The most common factors that have negative effects on adherence were reported by five studies [9-11,13,14] These are condition-related factors like the case of patients with baseline headache and depression, psychiatric disorders, leukopenia or anemia, thyroid gland dysfunction and genotype of HCV. Meanwhile, the therapy-related factors which have negative effects on adherence encompass side effects of combined PegIFN and RBV therapy, which was identified by only one study. [10]

In addition, Evon et al. [9] identified several social and economic factors. They reported that patients who have low education, are unemployed, lack public or private insurance, and are unmarried are more likely to miss doses of RBV. As regards the patient-related factors, it was found that being young in age had negative effects on adherence. [9] Tanioka et al. [13] found that being male and young in age has positive effect on adherence of the patient to treatment. Ravi et al. [10] reported on health care system-related factors that negatively influence adherence, e.g., delay in receiving prescription. Additionally, Tanioka et al. [13] reported that more patients in the one center have positive effect on adherence of the patients to treatment, which they attributed to the associated high experience of the physicians in handling patients with hepatitis C in such centers. No studies reported on patient's-related factors such as knowledge, attitudes, beliefs, perceptions, and expectations of the patient.

The highest adherence rates were reported by Evon et al. [9] and Re III et al. [11] who used the Medication Event Management System (MEM) and pharmacy refill data, respectively, to assess adherence.

The reported adherence by Evon et al. [9] to PegIFN and RBV during 24 weeks were 90.2% and 85% respectively. As well, Re III et al. [11] stated adherence to PegIFN was 95.4% and RBV was 86.1%during 24 weeks. In contrast, Ravi et al. [10] used a self-reported questionnaire and pill counting to evaluate adherence and reported low percentages of adherence to PegIFN treatment, RBV treatment, and a combination of these two treatments over the first 24 weeks of therapy. The reported ranges of adherence percentages were 35.4-65.8%, 46.3-56.8%, and 28.4-51.1%, respectively. On the other hand, Tanioka et al. [13] and Marti`n-Santos et al. [14] did not report the adherence measurement method which they employed.

Limitations of the review: This systematic review has some limitations. Firstly, this review could not include relevant literature published in other languages than the English language. Secondly, we only included studies that evaluate adherence to treatment of the HCV patients treated with PegIFN and RBV. Thirdly, few studies were included in this review because we excluded all the studies which did not have data on adherence to treatment of the hepatitis C patients.

CONCLUSION

There are many factors that have an influence on adherence of the hepatitis C patients to treatment. Managing these factors, especially in clinical centers, is very important for achieving good adherence to the hepatitis C treatment where the endpoint of therapy is SVR. Once the SVR is obtained, the infection is cured in more than 99% of the patients.

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