

Decrease of Hepatitis C Burden in Patients With Transfusion Dependent Beta Thalassemia Major, Thalassemia Research Center, 1995 – 2014

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Received: February 14, 2015; Revised: June 10, 2015; Accepted: July 5, 2015

Background: Chronic hepatitis C infection used to be one of the most important burdens on patients with transfusion-dependent beta thalassemia major (TDTM). Chronic active hepatitis reduces quality of life, and liver cirrhosis and cancer shorten life expectancy in many cases.

Objectives: We compared the characteristics of our patients at the Thalassemia Research Center (TRC) regarding hepatitis C infection at two time points.

Patients and Methods: A review was conducted in a cohort of 390 TDTM patients with a history of at least one blood transfusion in 2014. Type of treatment protocol for hepatitis C virus (HCV) and the number of courses were defined. Descriptive statistics were performed using SPSS software (V16).

Results: Screening for HCV started in 1995 at the TRC. Seventy-seven (15%) patients were antibody-positive in 1995. Tests for virus detection were not available at the time. Patients have been examined using serum AST, ALT, bilirubin, PT, PTT, and liver biopsy, and 45 were treated using alpha interferon alone. A second liver biopsy was performed at the end of treatment for 21 patients, and a blinded pathologist compared the histology according to the Knodell score. According to normalization of liver enzymes, the treatment was successful (McNemar test, $P < 0.02$). Based on the Knodell score, 54%, 31%, and 11% had complete, partial, and no response, respectively. A quantitative test for viremia became available thereafter. Thirteen patients who were resistant to alpha interferon have been treated using "Pegasys"TM ± ribavirin. Ten patients responded; however, three have been resistant and are still viremic. Twenty-seven patients received no treatment. Twenty-two (81.4%) had negative PCR tests. Five viremic patients refused treatment. A second screening test for HCV antibody was introduced in 2001, and, since then, annual screening for HCV antibody has been performed for all patients. No new case has been found since 2001. During the follow-up period, two deaths have been recorded in the cohort; none was a direct consequence of liver disease. Both patients had negative PCR tests for viremia. In 2014, there were 72 patients (52% men) with positive antibody tests, with a mean age of 30.5 ± 5.7 years. They mean age at the first blood transfusion was 2.8 ± 2.5 years. At the time of publishing, 15 patients (3.8%; 95% confidence interval 2 - 5.6) had viremia. Five patients had documented liver cirrhosis.

Conclusions: The prevalence of hepatitis C virus has decreased dramatically owing to primary prevention (donor blood screening and discarding infected blood) and antiviral treatment of affected patients. Better clinical management with iron chelating agents and supportive therapy for cirrhotic patients is also in place.

Keywords: Hepatitis C Virus; Treatment; Iran

1. Background

Hepatitis C virus (HCV) used to be the main cause of transfusion-related infectious disease in transfusion-dependent beta thalassemia major (TDTM) in IR Iran. Alavian et al. reported that the odds ratio for the likelihood of positive serology for HCV infection was 28.9 (95% confidence interval [CI] 18.9 - 44) in patients with beta thalassemia major compared with the general population (1). Detection of HCV antibody became available worldwide in 1992, and screening for infected donors started began in 1996 in The Iranian National Blood Transfusion Organization of Iran (INBT) (2). Many reports are available regarding the prevalence of HCV

infection among patients with beta thalassemia major in different parts of the country (2-16). The rate of infected patients with an acceptable sample size has been reported to range from 8% (15) to 39.7% (9). Alavian et al. conducted a systematic review in 2010 and reported that the pooled estimate of positive anti-HCV serostatus in 5,229 TDTM patients living in Iran was 18% (95% CI 14 - 21) (1). Our first screening conducted in 1995 with ELISA (second generation) confirmed RIBA (Western blot) in INBTO. Five hundred patients were tested, and 15.4% (95% CI 12.3 - 18.5) were infected with HCV (3). This paper was not included in the review. Regarding anti-

ral therapy, interferon was the first introduced medication. A combination therapy with pegylated interferon alpha and ribavirin was then considered the standard treatment for HCV (17). New antiviral agents such as boceprevir have recently been approved specially for HCV genotype 1, which is especially difficult to treat. Guidelines for treatment and follow-up of HCV-infected patients in Iran have been developed and were published in 2012 (17).

2. Objectives

This is a report of how the trend of HCV infection has changed in patients in the Thalassemia Research Center (TRC), Mazandaran University of Medical Sciences, from 1995 to 2014.

3. Patients and Methods

This descriptive study was performed by reviewing existing medical records. TRC patients have had the same medical records since 1980. Medical records of patients both alive and dead with a definitive diagnosis of TDTM at the TRC were reviewed. Patients with a history of at least one blood transfusion were included. The date of birth, sex, age at first blood transfusion, and diagnosis of HCV infection were extracted. Infection was defined as the presence of HCV antibodies. The type of treatment protocol and the number of courses were extracted. Confidential measures were adapted regarding names and addresses.

Descriptive statistics, frequencies, and standard deviations were performed using SPSS software (V16).

4. Results

Screening for HCV started in early 1995 in the TRC. In 1995, of 500 patients, 77 (15.4%; 57% men) with a mean age of 13.5 ± 4.6 years were antibody positive (second-generation ELISA test). Tests for virus detection were not

available at the time. Patients have been examined by measuring serum AST, ALT, bilirubin, PT, PTT, and liver biopsy. Eighty-seven percent had chronic active hepatitis, and 11% already had liver cirrhosis. Forty-seven cases were treated using alpha interferon (Sandoz pharmaceutical). A second liver biopsy was performed at the end of treatment for 21 patients, and a blinded pathologist compared the histology according to the Knodell score. According to normalization of liver enzymes, the treatment was successful (McNemar test, $P < 0.02$). Based on the Knodell score, 54%, 31%, and 11% had complete, partial, and no response, respectively (3). Further examination revealed that the predominant genotype of HCV in our center was 1a, as in other parts of the country (2). Annual screening for HCV was routinely conducted for all patients since 1995. After introducing the pegylated interferon, 13 patients who were resistant to alpha interferon have been treated in Tehran with "Pegasys"TM + ribavirin; since then, positive quantitative PCR was the main index for treating patients. In 2014, a cohort of 390 TDTM patients born between 1937 and 2012 was under treatment at the TRC. Among 92 patients born after 1996, none were infected with HCV. Seventy-two patients were infected with HCV. Table 1 shows the characteristics of affected patients in 2014. Seventy-two TDTM patients, 52% men, with the mean age of 30.5 ± 5.7 years are under follow-up. The mean age at the first transfusion was 2.8 ± 2.5 years.

Two deaths occurred in the cohort. The cause of death in one patient was disseminated chicken pox infection. He was treated with alpha IFN only, with a negative PCR test. The other patient had severe cardiomyopathy. He was treated with "Pegasys"TM + ribavirin; however, the last PCR test was negative. At the time of publishing, 15 patients (3.8%; CI 95% 2 - 5.6) had viremia. All patients with viremia who have not been treated are aware of their situation. There are five patients with documented liver cirrhosis including three patients with viremia.

Table 1. Transfusion-Dependent Beta Thalassemia Major Patients According to HCV Status, TRC, 2014^a

All Infected Patients (n = 72)	Last Quantitative HCV RNA	
	Positive	Negative
Treated with alpha IFN only (n = 32), 17 women and 15 men	7	25
Treated with alpha IFN followed by Pegasys TM + ribavirin, (n = 13), 4 women and 9 men	3	10
Not treated so far (n = 27), 14 women and 13 men	5	22
Total	15	57

^a Abbreviation: HCV: hepatitis C virus.

5. Discussion

The study objective was to compare the prevalence of HCV infections at two different times in patients with beta thalassemia major. A dramatic reduction in HCV burden has been shown in our center. Epidemiology of HCV infection is changing worldwide (1). HCV infection incidence has declined in developed countries owing to safe blood products, the effect of so-called harm reduction programs, and control of transmission through intravenous drug abuse (1). In some countries, after better screening of blood products, the main increase in HCV prevalence is due to increase of IV drug abuse. The prevalence of HCV infection in the general population of Iran is less than 1% (1). In underdeveloped countries, HCV prevalence remains high. Alavian et al. conducted a systematic review regarding HCV infection in the general population of Iran (18). Eight eligible studies from six provinces with residents representing about 435 of the country's population showed a prevalence rate of 0.16% (95% CI 0 - 0.59), one of the lowest rates among developing countries (18).

Mazandaran is among the provinces with a 0.05% infection rate among blood donors, but no research has been published in the general population (2, 18). Moreover, concerning the patient-to-patient transmission of HCV, Samimi-Rad et al. suggested that nosocomial transmission was responsible for infection in some of their cases in the thalassemia wards of Tehran and Amol (19).

There has been progress in the last 19 years, as follows:

- 1- Successful preventive measures have reduced the number of new patients dramatically (20).
- 2- Better management of patients has led to prolonged survival (21).
- 3- Donated blood has been screened and infected blood discarded (2).
- 4- Effective antiviral agents have emerged (18).

All the above achievements have changed the disease burden. The burden of HCV has decreased mainly because of primary prevention (donor blood screening and discarding infected blood) as well as antiviral treatment of affected patients. Chronic management of resistant patients with iron chelating agents and supportive therapy are also in place.

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