From A to Z

On Hepatitis C in Thalassemia

Comprehensive Guidelines for Medical Professionals

Edited by:

Seyed Moayed Alavian M.D,

Professor of Medicine, Gastroenterologist and Hepatologist,Director Middle East Liver Disease Center

IN THE NAME OF

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Comprehensive Guideline for Medical Practitioners

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Preface

Thalassemia patients have a high prevalence of hepatitis C virus (HCV) infections. Recent improvements in the survival of these patients are a result of more services for the control of iron overload, the provision of safe blood, and better control of complications. Today, liver disease is the main cause of mortality in thalassemia patients throughout the world. Unfortunately, there are inadequate policy in most thalassemia centers for the control of HCV infections. Thalassemia patients with HCV infections pose a real dilemma in the management of this infection, and they must have access to adequate professional counseling from health care workers, in addition, the health system should provide appropriate diagnostic and therapeutic options. Therefore, I considered it imperative to provide a book from A to Z for health professionals regarding the epidemiology, screening, diagnosis and treatment of HCV infection in this high risk group. My hope is for improvements in the control of HCV in thalassemia patients in the world, especially in the Mediterranean region.

Chapter 1

Virology

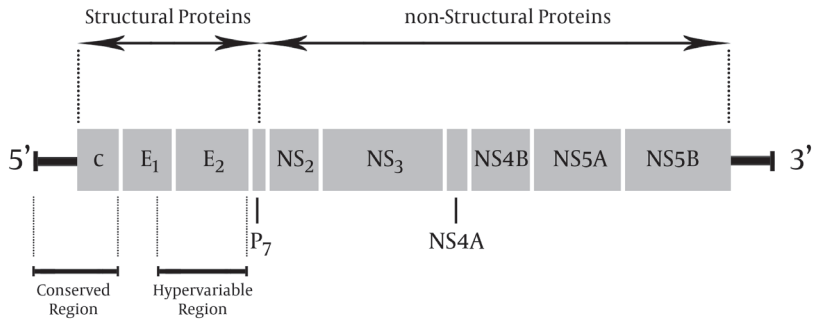
The virus was discovered and characterized by Choo et al. in 1989 (1) by using molecular biology techniques from a chimpanzee infected with the sera of a patient with chronic non-A, non-B hepatitis. Their data indicated that this clone was derived from the genome of the Non-A, Non-B Hepatitis (NANBH) agent and was similar with the agents belonging to the Togaviridae or Flaviviridae viral families (1). Therefore, significant advances in molecular biology have allowed the scientists to explore the details of the virus and to develop a wide variety of antigens and synthetic peptides that have been successfully deployed in immunoassays to detect Hepatitis C virus (HCV) infection.

Hepatitis C virus is an enveloped positive-sense single-stranded RNA virus and the only member of the genus Hepacivirus within the Flaviviridae family. The genome contains a single-stranded RNA, large open reading frame (ORF) with a size 9.4 kb in length and a highly conserved untranslated region (UTR) at the 5' and 3' ends (2) (Figure 1.1). The HCV genome encodes for a viral polyprotein of approximately 3010 amino acids, which

is cleaved after translation to yield 10 viral proteins (3).

The 5'end of its genome consists of an untranslated region containing an internal ribosome entry site and three structural genes, the core region, C, which codes for the nucleocapsid, and the envelope regions, E1 and E2, which code for envelope glycoproteins. The 5'untranslated region and core gene are highly conserved among genotypes, but the envelope proteins are coded by the hypervariable region, which varies from isolate to isolate and may allow the virus to evade the immunological response of the host. Genotype-specific sequence differences exist in the 5' UTR, while the secondary and tertiary structures are essentially preserved. The 5' UTR is required for replication of the negative strand. A liver specific micro-RNA, miRNA-122, with binding sites in the 5' UTR, has been shown to facilitate HCV replication (4).

Figure 1.1 Hepatitis C genome



The 3' end of the genome also includes an untranslated region and contains the genes for six non-structural (NS) proteins NS2, NS3, NS4A, NS4B, NS5A, and NS5B. The NS2 protein is a cysteine protease that cleaves the NS2/3 junction and the NS3-4A serine proteases cleave all the downstream proteins from the glycoprotein. Important NS proteins involved in viral replication include the NS3 helicase, NS3-NS4A serine protease, and the NS5B RNA-dependent RNA polymerase. The structural proteins are cleaved from the polyprotein by the viral proteases NS2 and NS3. There is evidence for long-range RNA/RNA interactions between the 5' and 3' UTRs, as well as between the 5' UTR and RNA sequences at the C-terminal of NS5B. These interactions play an essential role in the replication process. Replication of HCV does not need the DNA intermediate and it does not integrate into the host genome. Particles of HCV circulate in a relatively low titer, but

their replication has a very high daily rate, with a half-life of 2.7 hours.

There are at least six genotypes of HCV, and more than 50 subtypes within these genotypes, as well as diverse populations of quasispecies within each infected individual, that have been identified by nucleotide sequencing (5). The source of this variation, like that of other RNA viruses, is the high mutation rate of its error prone RNA polymerase during the HCV replicative process. Shortly after its discovery in 1989, it became clear that HCV had a substantial nucleotide sequence diversity, with only 66–80% overall sequence similarity among strains belonging to different genotypes or subtypes (6). The HCV isolates show four levels of genomic variations: types, subtypes, isolates, and quasispecies. The overall sequence similarities over complete genomic sequences are of at least 91% within quasispecies, approximately 79% (77–80%) between subtypes, and about 68% (66–69%) between different types. This quasispecies is composed of a group of heterogeneous RNA sequences centered on a dominant nucleotide sequence that changes, throughout the course of the infection, under the selective pressure of the host immune system. More than one genotype can be found in the circulation of some HCV-infected patients, particularly in individuals who have received multiple transfusions and intravenous drug users. These are referred to as mixed-genotype infections (7-10).

The HCV genotype has been shown to present unique patterns of geographical distribution and to be a major research instrument in HCV epidemiological studies. In recent years however, a shift in the prevalence of predominant HCV genotypes has been observed in a number of European countries (11-16), in correlation with variations in the modes of HCV acquisition. Different HCV isolates worldwide show substantial nucleotide sequence variability throughout the viral genome. The polymerase chain reaction (PCR) analysis with type-specific primers for identification of the HVC genomic typing enables the separation into six major genotypes (1 to 6) and a series of subtypes (e.g. a, b, c) (17-20). These viral types and subtypes differ in their geographical distribution and antigenicity. Types 1, 2 and 3 are distributed almost worldwide (21-27). Types 4, 5 and 6 have been found in distinct geographical areas (17, 25, 26, 28). Interestingly, not only do the HCV genotypes seem to differ in nucleotide sequence and geographical distribution, but there is also evidence of biological differences between the three HCV genotypes. Patients with HCV subtype 1b have a poorer response

to interferon-alpha treatment. The transmission route may also affect the distribution of HCV genotypes.

Conclusion remarks

• The HCV particles circulate in a relatively low titer but their replication has a very high daily rate, with a half-life of 2.7 hours. The HCV genome encodes for a viral polyprotein of approximately 3010 amino acids, which is cleaved after translation to yield 10 viral proteins;

• The replication of HCV does not need the DNA intermediate and it does not integrate into the host genome;

• There are at least six genotypes of HCV, and more than 50 subtypes within these genotypes, with different geographical distribution.

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Chapter 2

Epidemiology

Introduction

Hepatitis C virus (HCV) has been discovered in 1989 and it is a major cause of liver related morbidity and mortality worldwide, representing a major public health concern, especially during the recent years (1, 2). The average prevalence of HCV infection throughout the world is of 2–3% or 170–200 million persons (3-7). These estimates are often based on volunteer blood donor prevalence rates and may therefore underestimate the true prevalence. Also, the surveys in general populations may have failed to include some high risk groups. Nonetheless, these estimates provide some idea of the worldwide pattern of infection. Overall and age-specific prevalence varies considerably from country to country. The antibody prevalence is low (0.01–0.1%) in the United Kingdom and Scandinavia, slightly higher (0.2–1.8%) in the Unites States, Western Europe, Australia, and parts of South America and Africa, and intermediate (1–5%) in Eastern Europe, the Mediterranean, Middle East, Indian subcontinent, Brazil, and

parts of Africa and Asia (8). The highest prevalence is in northern Africa, 6% in Zaire (8), 7.9% in Libya (9), and 17–26% in Egypt (8, 10, 11). The prevalence is also high in some areas of Saudi Arabia (12).

The HCV infection is highly prevalent among thalassemia patients, especially in developing countries, and the rate of infection varies markedly from country to country (13). Thalassemia is one of the most common genetic disorders. It is estimated that 300.000 infants with major hemoglobinopathies are born worldwide each year, of whom 60.000–70.000 are beta thalassemia (β-thalassemia) major cases, especially in the Mediterranean area, Middle East, Far East, and East Asia (14-16). Although thalassemia mostly affects developing countries, there is limited knowledge of its accurate frequency and distribution in these regions. Knowing the prevalence of thalassemia and characterizing the clinical features and demography of patients will enable us to properly measure the burden of disease. Thalassemia is characterized by decreased or absent globin chains production. The resultant anemia is caused by the destruction of the erythroblasts in the bone marrow, peripheral hemolysis of the erythrocytes and ineffective erythropoiesis. The life-long need for blood transfusions to maintain a hemoglobin level of at least 9.5 g/dl renders these patients vulnerable to transfusion transmitted viral infections, especially HCV (13). Over the last 20 years, management for thalassemia major has improved to the point where we predict that the patients' life expectancy will approach that of the normal individuals. These outcomes are the result of safer blood transfusions, the availability of three iron chelators, and new imaging techniques that allow specific organ assessment of the degree of iron overload (17). Although regular blood transfusions improve the overall survival of patients with β-thalassemia, they carry a definite risk of infection with blood-borne viruses (18).

Epidemiology

The HCV infection represents a major, worldwide health issue (19). It is estimated that over 170–200 million people are infected and the virus is distributed worldwide with prevalence varying widely between different regions from 0.2–40% (20, 21). While rigorous donor screening, testing pro-

cedures and suitable donor selection programs have dramatically reduced the transmission of HCV via transfusion of blood products, there are still many countries in which standards of blood product management do not adequately ensure the protection of chronically-transfused patients, especially thalassemia patients, from this complication (2, 22, 23).

The prognosis and survival of patients with thalassemia major has dramatically improved in the last two decades due to regular blood transfusions and chelation therapies (24-26) and the main factors that correlated with an increase in the hazard ratio for death were represented by cirrhosis, arrhythmia, previous episode of heart failure, diabetes, hypogonadism, and hypothyroidism (27).

The HCV infection is a widespread disease affecting a large number of thalassemia patients worldwide and is considered a major public health problem in this high risk group. While rigorous donor screening, testing procedures and suitable donor selection programs have dramatically reduced transmission of HCV via transfusion of blood products, pitfalls in the management of blood products in many countries account for the increased rate of HCV infection (2, 13, 23, 28). The prevalence rate in polytransfused thalassemic patients in different settings increases to up to 60% globally (22, 29-37), but there are tremendous discrepancies between epidemiological studies.

Middle East and EMRO countries status

There is heterogeneity regarding the prevalence of HCV infection in Eastern Mediterranean region. For example, the HCV infection rate ranges from 2–32% in Iran and from 33–93% in Saudi Arabia. Most of these studies also have the drawback of inadequate sample size. In some countries such as Egypt and Jordan, the publication date of available data backs to one or two decades ago and updated data are unavailable.

In a meta-analysis in the Mediterranean and Middle East area on seroepidemiology of HCV infection in thalassemia patients in the EMRO countries, there were 45 relevant published articles that evaluated anti-HCV antibody serostatus in thalassemia patients from EMRO countries (Table 2.1). Unfortunately, no data were available from the following countries:

Table 2.1. Study and patient characteristics from Iran

Ref. No.	Author	Publication year	Design	province	Sample size	ELISA	RIBA	Mean age	Male (%)	Prevalence (95% CI)
(48)	Alavian et al.	2003	Census (C-C)	Qazvin	95	2nd	Yes	12±7	48%	24% (15-33)
(49)	Mirmomen et al.	2001	C-S	Tehran	410	2nd	No	22.4 ± 7.8	61%	27% (23-31)
(50)	Alavi et al.	2005	C-S	Tehran	110	2nd	Yes	11.5±5.2	50%	11% (5-17)
(22)	Mirmomen et al.	2006	C-S	Tehran, Zanjan, Qazvin, Semnan, Kerman	732	3rd	Yes	17.9 ± 9.0	56%	19% (17-22)
(51)	Bozorghi et al.	2008	Census (C-S)	Qazvin	207	3rd	Yes	14.29±6.5	50%	26% (20-32)
(52)	Kompani et al.	2008	C-S	Khuzestan	195	2nd	No	14.9±6	50%	21% (15-27)
(53)	Ghafourian et al.	2009	C-S	Khuzestan	206	3rd	No	16.4±6.42	47%	28% (23-33)
(36)	Tamaddoni et al.	2007	C-S	Mazandaran	113	3rd	No	15.8±8.93	43%	11% (5-17)
(54)	Ameli et al.	2008	C-S	Mazandaran	65	3rd	No	19.5±8.9	NR	17% (10-24)
(55)	Shariatzadeh et al.	2000	C-C	Markazi	54	2nd	Yes	Range (1-36)	NR	9% (1-17)

(35)	Samimi-Rad et al.	2007	C-C	Markazi	98	3rd	Yes	12.4	51%	5% (1-9)
(56)	Mahdaviani et al.	2008	Census (C-C)	Markazi	97	3rd	Yes	13.1±7.3	51%	7% (2-12)
(34)	Ansari et al.	2007	C-S	Fars	806	2nd	No	15.3±6.82	50%	14% (12-16)
(57)	Akbari et al.	2007	C-C	Fars	200	2nd	Yes	15.2±6.3	50%	25% (19-31)
(37)	Karimi et al.	2001	C-S	Fars	466	2nd	Yes	12.3 ± 5.0	52%	16% (13-19)
(58)	Kadivar et al.	2001	C-S	Fars	147	2nd	Yes	13.6±4.8	55%	27% (20-34)
(59)	Javadzadeh-Shahshahani et al.	2006	Census (C-C)	Yazd	85	2nd	Yes	12.6±7.56	48%	9% (3-16)
(60)	Hariri et al.	2006	Census (C-S)	Isfahan	616	3rd	Yes	15.5±8	NR	11% (8-12)
(61)	Faranoush et al.	2006	Census (C-S)	Semnan	63	2nd	No	11.8±4.7	60%	40% (28-52)
(40)	Zahedi et al.	2003	Census (C-C)	Kerman	100	2nd	Yes	11.5±5.7	45%	31% (24-38)
(62)	Sanei-Moghaddam et al.	2004	C-S	Sistan and Baluch-istan	364	2nd	Yes	9.7±5.2	57%	13% (10-16)

ELISA = enzyme linked immunosorbent assay, RIBA = recombinant immunoblot assay

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Table 2.2. The HCV infection rates among polytransfused thalassemia patients from EMRO counties other than Iran.

Country	Author Name	Publication year	Design	Sample size	ELISA	RIBA	age	Male (%)	Prevalence (95% CI)
Iraq	Al-Kubaisy et al. (41)	2006	C-S	559	3rd	Yes	2-10	NR	67% (63-71)
Pakistan	Akhtar et al. (63)	2004	C-S	256	3rd	No	NR	NR	34% (28-40)
	Mohammad et al. (64) *	2003	C-S	80	3rd	No			36% (25-47)
	Younus et al. (65)	2004	cohort	75	3rd	No	6.5	64%	42% (31-53)
	Burki et al. (66) *	2005	C-S	180		No			42% (34-48)
	Shah et al. (67)	2005	C-S	250	NR	No	5-10 (43%)	72%	57% (51-63)
	Moatter et al. (68)	1999	C-S	100	2nd	No	8	57%	34% (25-43)
	Mukhtar et al. (69)	2005	C-S	250		No			57% (50-62)
	Hussain et al. (70) *	2008	C-S	180	NR	No	7	NR	42% (34-48)
Bahrain	al-Mahroos et al. (71) *	1995	C-C	242		No			32% (26-38)
Kuwait	Al-Fuzae et al.	1998		129					33% (23.9-40)
Jordan	Al-Sheyyab (39)	2001	C-S	143	NR	No	9	61%	40% (32-48)
Lebanon	Ramia et al. (72) *	2002	C-S	395		No			14% (10-16)
Saudi Arabia	Bahakim et al. (73) *	1991	C-C	78		No			33% (23-43)
	al-Fawaz et al. (74)	1996	C-C	28		No		51%	57% (39-75)
	Al-Hawsawiet al. (75) *	2000		32					91% (80-100)
Egypt	el Gohary et al. (76)	1995	C-C	45	2nd	No	NR	NR	76% (64-88)
	el-Nanawy et al. (77) *	1995	C-C	18		No			44% (21-67)
Libya	Daw et al. (78) *	2002	C-C	250		No			11% (7-15)

ELISA = enzyme linked immunosorbent assay, RIBA = recombinant immunoblot assay

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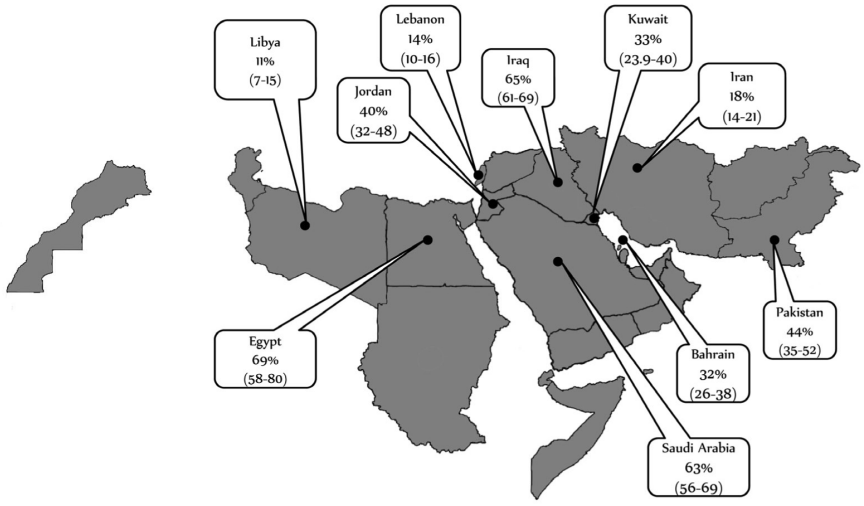
Djibouti, Morocco, Somalia, Sudan, Syria, Emirate, Oman, Qatar, Yemen, West Bank and Afghanistan. There were 21 studies involving 5229 subjects from Iran, eight studies including 1371 subjects from Pakistan, three and two studies with 138 and 42 subjects from Saudi Arabia and Egypt, respectively. Only one study was identified from Bahrain, Iraq, Kuwait, Jordan, Lebanon and Libya (Table 2.1). Mean age of subjects ranged from 9.7–22.4 years of age. Gender distribution ranged from 43–61% male (13). The pooled HCV infection rate was 45% in Pakistan, 63% in Saudi Arabia, 18% in Iran and 69%in Egypt (13). The infection rate among thalassemia patients in countries where only one report was available ranged from 11–14% in Libya and Lebanon to 65% in Iraq (Figure 2.1).

Figure 2.1 Geographical distribution of pooled or individual epidemiology of HCV infection among thalassemia patients in EMRO



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The thalassemia patients, which represent a high risk group for HCV infection, act as a reservoir of this infection and are one of the main obstacles for HCV infection control in the community. The heterogeneous pattern of the geographical distribution of HCV infection in thalassemia patients indicates that the safety of blood before blood screening varies in different countries and may be related to the different infection prevalencies and to risk factors in blood donors and the general population (22). First transfusion before or after introduction of blood donors screening for anti-HCV an-

tibody was the major determinant of HCV infection in the region. In Kuwait and Jordan, all thalassemia patients transfused were at risk of HCV infection before blood donors screening (1992 in Kuwait and 1995 in Jordan) (38, 39). In Iran, blood donors screening for HCV infection started in 1996. The pooled odds ratio (OR) of HCV infection rate for patients who were transfused before that date was OR: 7.6 (95% CI, 4.7–12.3). This implies an increase in blood safety and more health precautions attention in Iran (22, 35, 40), but data from other EMRO countries are inadequate and inconclusive.

In conclusion, transfusion transmitted diseases are major challenges for the health of patients with hematologic disorders who need to receive regular blood products. Improvement in screening of blood products during 1990s has dramatically decreased the risk of transmission of blood borne diseases via transfusion; however, recent studies have demonstrated that the prevalence of blood borne infections like hepatitis B and C still represent a problem (41-43).

Transmission of HCV

Hepatitis C virus is the second most common cause of chronic hepatitis worldwide and the most common cause of chronic liver disease in areas of the world where hepatitis B virus (HBV) is not endemic. The HCV is transmitted from person to person via blood transfusion, intravenous drug use, and other parenteral exposures. Prior to the development of a screening test for HCV in the early 1990s, the risk of developing non-A-non-B hepatitis from a blood transfusion was 5–10%. Since the development of the anti-HCV assay and the universal screening of all donated blood, the risk of developing HCV following a blood transfusion has declined from about 1:250.000 to 1:500.000. The most common mechanism by which HCV is currently transmitted is represented by the contaminated needles used by intravenous drug users, followed by a break in universal precautions in patients receiving medical care and from the use of reusable and non-sterilized medical equipment in underdeveloped countries. In contrast, the risk of sexual and vertical transmission, although possible, is low, except in individuals with high-risk sexual behaviors and multiple partners and in the setting of HCV-HIV co-infection.

Acute HCV infection is parenterally-acquired and may occur after transfusion of unscreened blood or blood products in thalassemia, as a residual risk. Spontaneous clearance of acute HCV occurs with a high rate within the first 12 weeks of infection and depends on the age the person who acquires the infection (44, 45). The younger the age of infection, the higher is the spontaneous clearance rate of HCV (Unpublished data from the author: about 50% of spontaneous seroconversion of acute HCV in children). The spontaneous clearance rate of HCV in North American thalassemia patients is 33% (46). Because infection with HCV results in chronic infection in a large proportion of infected individuals, it has been suggested that early treatment of acute HCV may limit the development of chronic hepatitis (28).

I would like to sensitize my colleagues about the probability of transmission of HCV infection from patient to patient in thalassemia centers and that the eradication of the virus can prevent nosocomial transmission (13, 35, 47).

clusion remarks

- Up to 60% of adult thalassemia patients are infected with HCV infection in the world.

- There is a strong gap in current knowledge about blood safety in Eastern Mediterranean countries. The data were available from 50% of the countries in this region and most of these data had limitations concerning the low sample size and were outdated. The lack of knowledge about blood safety and current serostatus of HCV infection, as the most prevalent transfusion transmitted disease in thalassemia patients, is a major threat to the public health in these countries.

- The heterogeneous pattern of the geographical distribution of HCV infection in thalassemia patients throughout the country indicates that the safety of blood before blood screening differed between provinces and may be related to different prevalence of HCV

infection and risk factors in blood donors and general population.

• Acute HCV infection should be treated as soon as possible in adult thalassemia patients.

• The integration of a surveillance system for periodic checking the HCV infection in all thalassemia patients and reporting the new cases to the ministry of health for follow-up and finding the origin of new infections are strongly recommended.

• Patient to patient transmission of HCV in thalassemia patients should be considered as an important route for horizontal infection and eradication of the virus can prevent this nosocomial transmission.

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Chapter 3

Natural History

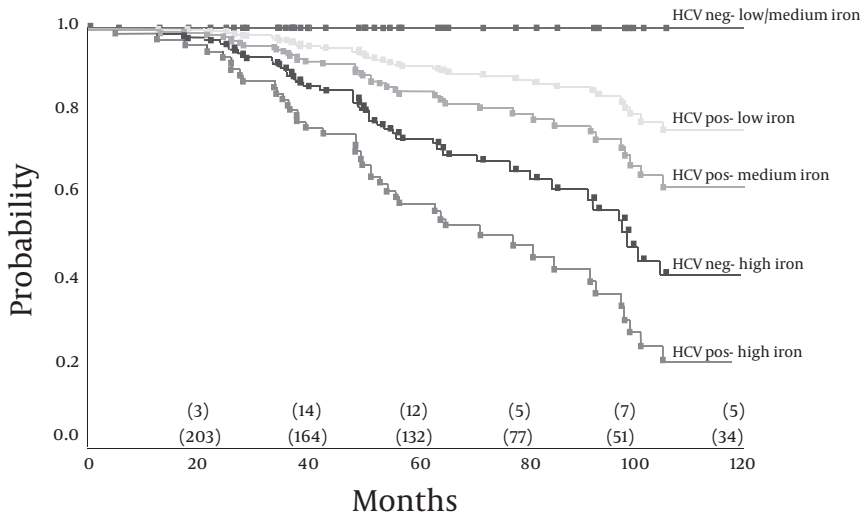
Introduction

The majority of HCV-infected patients are asymptomatic, and nowadays the infection is usually detected via screening programs. The natural history of chronic hepatitis C in cohort studies is difficult to define and it can be variable. There are many biases which affect study results such as; those inherent in referral populations, difficulty in establishing the onset of the infection, and limited periods of follow-up (1). Unfortunately no prospective studies exist in which an entire population of infected individuals had been identified at the time of infection and followed systematically over an adequate time period. Based on currently available data different courses of natural history emerge and they depend on; the population studied, duration of the infection in that particular population, how the disease was transmitted, and the relative prevalence of cofactors including gender, age at onset of infection, and alcohol consumption. Older age at HCV exposure,

male gender (2, 3), non-white race (4, 5), higher body mass index (6), and heavy alcohol intake (>40-50 gm/day) (2, 7-11), have been variously identified as factors associated with a more rapid disease progression (12-15). Increased quasi-species diversity in HCV (16, 17), HBV, HIV coinfection (18-22) and cigarette smoking are other factors which affect disease progression.

Although the natural history of chronic HCV infection in patients with thalassemia is unclear, the morbidity and mortality of those patients is thought to be higher. Liver disease is more severe in HCV-infected patients and this may be compounded by hepatic siderosis (23, 24). The prevalence of liver cirrhosis in thalassemia patients with a HCV infection depends on the level of iron chelation in the population studied and it has been reported to be present from 10% to 20% in several studies (25-27) (Figure 3.1).

Figure 3.1. HCV in thalassemia: the importance of iron overload on fibrosis progression



The figure is extracted from the article by Angelucci E et al (26) with permission

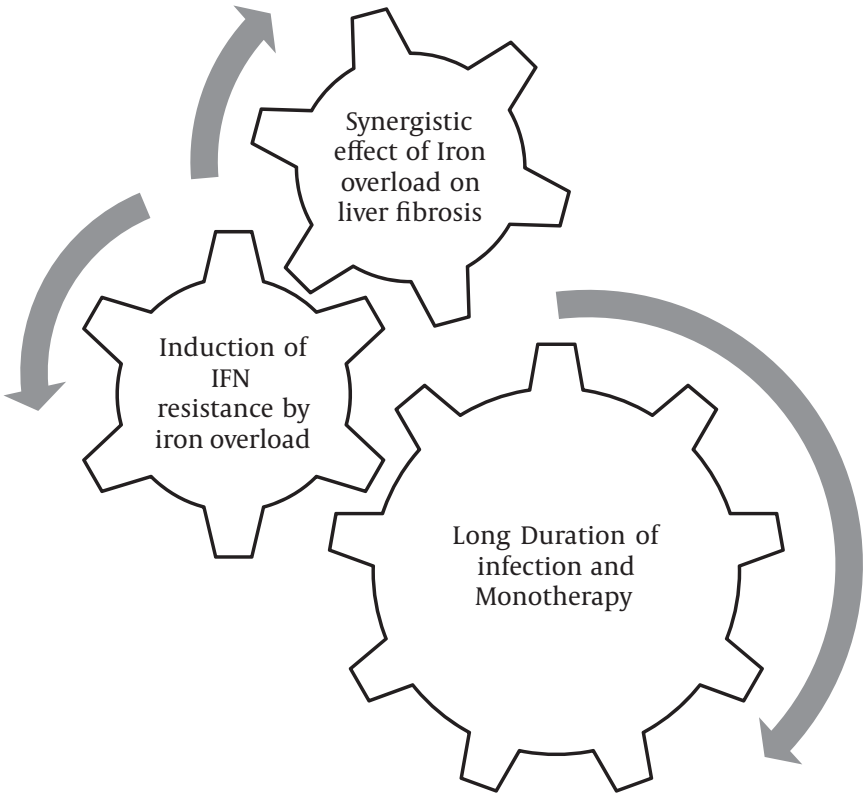
Iron overload and HCV infection are independent risk factors for liver fibrosis progression, and their concomitant presence results in a striking increase in risk (26). Male gender, higher alanine aminotransferase (ALT) levels, the existence of an HCV infection, and higher iron concentrations in the liver were significantly associated with severe fibrosis and cirrhosis

(25-28). Hepatitis virus C infection is the main risk factor for liver fibrosis in transfusion-dependent thalassemics. Adequate chelation therapy usually prevents the development of liver fibrosis in thalassemics who are free of a HVC-infection and it also reduces the risk of developing severe fibrosis in thalassemics with chronic hepatitis C.

Iron Overload

Transfusion therapy has greatly improved the survival of transfusion dependent thalassemia major (TM) patients; however, the resultant iron load damages tissues including the heart, liver and endocrine organs. Among these, heart complications still remain the leading cause of mortality in thalassemia major patients who receive transfusion and chelation therapy (29) (Figure 3.2).

Figure 3.2. Why thalassemia patients with HCV infection are very special population?



Close monitoring of individual organ iron concentrations and functioning are thus important for the optimization of individual patient care (30). The ability to determine the amount of iron in the liver and heart by magnetic resonance imaging allows the prescription of the most appropriate chelation regime for these patients and to reassess what the aims, with respect to total body iron, should be. Iron deposits in the liver in thalassemia patients due to chronic hemolytic anemia leads to; tissue damage, collagen formation, portal fibrosis, and progression to liver cirrhosis (31, 32). Hepatocellular carcinoma (HCC) formation is often observed following the formation of severe fibrosis and liver cirrhosis (33). In prospective studies the existence of a HCV infection was the main risk factor for acquiring HCC in thalassemia HCV-infected patients (34, 35).

Recent evidence from Europe has shown that by normalizing iron stores not only are new morbidities prevented, but also reversal of many complications such as; cardiac failure, hypothyroidism, hypogonadism, impaired glucose tolerance, and type 2 diabetes can occur, and it also improves survival rates and patients' quality of life. All these advances in management require the absolute cooperation and understanding of parents, children, and ultimately, the patients themselves. Only with such cooperation can normal long-term survival be achieved, as adherence to treatment is now likely to be the primary barrier to longevity. Unfortunately despite improvements in the life expectancy of thalassemia patients through the use of transfusion and chelation therapy, most of the children born with thalassemia major in developing countries do not have access to sufficient chelation therapies and they often die due to complications of iron overload (29).

HIV and HCV Coinfection

Because HIV and HCV are transmitted in similar ways, it is expected that they will develop together. HIV and HCV infections are basic issues that health systems are faced with in many societies. However, the prevalence of HIV among HCV-infected patients varies according to the distribution of HCV risk factors, with the highest rates being seen in intravenous drug users (36). It is estimated that between 34–38.6 million people around the world are infected with HIV,

compared with 170–200 million by HCV, and 4–5 million people who are coinfected with HIV and HCV (37). Coinfection of HIV/HCV has a different natural history in comparison with mono-infected cases. HIV increases the progression of the HCV infection, it also increases HCV viral loads and the rate of progression to cirrhosis and hepatocellular carcinoma (38-40). Thalassemia patients have been found to be at higher risk of acquiring HIV-HCV confections and this problem was more prevalent in developing countries (41). Prevalence rates in countries with safer blood transfusion are close to zero and most of the infected patients resulted prior to screening (42, 43).

Hepatocellular Carcinoma

It has been recognized that the most important risk factor for HCC is cirrhosis (44) and iron overload is also a known risk factor for this condition. It seems that the numbers of thalassemia patients who develop HCC will increase in the future and it will be one of the leading clinical problems in thalassemia. It is therefore, reasonable to recommend HCC screening of all thalassemia patients with one or more risk factor since this would facilitate early treatment, leading to improved outcomes (33). Preliminary data suggests an incidence of HCC in thalassemia of about 2%. However, since thalassemia is endemic in many underdeveloped countries where patients are probably not screened for HCC, it is possible that the present knowledge of this issue represents only the tip of the iceberg. Iron chelation appears to play a protective role in the occurrence of HCC (45). There is currently a debate regarding the best treatment for HCC in thalassemia, and liver transplantation is considered a contraindication. Periodic liver ultrasound HCC screening should be considered for thalassemia patients with risk factors for HCC. Prevention of HCV infections through blood transfusion is nowadays, the only known evidence-based means to prevent HCC in thalassemia.

Concluding Remarks

• Iron depletion with iron chelators can stabilize or improve liver fibrosis and histological necroinflammation.

• Male gender, higher ALT levels, existence of a HCV infection, and higher iron concentrations in the liver are significantly associated with severe fibrosis and cirrhosis.

• HIV increases the progression of the HCV infection, increases HCV viral loads and the rate of progression to cirrhosis and hepatocellular carcinoma.

• Thalassemia patients with a HCV infection and liver cirrhosis should be put on surveillance for HCC with periodic liver ultrasounds every six months and alpha-fetoprotein level detection.

Referer

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Chapter 4

Diagnosis and evaluation

Serological assays

The first step in the diagnosis of HCV infection is the enzyme-linked immunosorbent assay (ELISA) for anti-HCV antibody, detecting past exposure or ongoing infection. Three generations of the ELISA have been developed; the ELISA-3 has a more than 99% sensitivity and specificity. The window for serologic conversion after initial exposure varies within a range of 20–150 days, with a mean of approximately 50 days. False-positive tests are most often seen in low-risk populations, such as blood donors. False-negative tests are most often seen in immunocompromised patients, as is the case of HIV positive subjects or on chemotherapy, also including dialysis patients and transplant recipients. For differentiation between past exposures from ongoing infection, evaluation of HCV RNA by polymerase chain reaction (PCR) is necessary (1-4). In ELISA-3 analyses, a recombinant NS5 antigen has been added to the four antigens used in the second-generation assays. These third-generation assays have a higher sensitivity and speci-

ficity than second-generation assays and suffer a less important influence from the infecting genotype.

The PCR

The second main step in the diagnosis of chronic HCV infection is the detection of HCV RNA in serum. Virus is generally detectable 7–21 days following exposure. There are three main assays available. Detection of HCV RNA by using amplification techniques such as PCR or transcription-mediated amplification (TMA) confirms the presence of ongoing infection with active HCV replication. The sensitivity of PCR for HCV RNA detection may vary according to the choice of primers and the handling of pre-extraction samples. Two different methods have been commonly used for the quantitation of HCV RNA and have become commercially available. The first was developed by Roche Diagnostics Systems (Branchburg, NJ, USA) and is based on a competitive PCR assay for HCV RNA quantitation (Roche Monitor assay). Quantitative HCV RNA by PCR is less sensible, but still able to detect as few as 100 copies/mL and is able to provide an absolute viral titer. It is currently reported as both copies/mL and as international units/mL (IU/mL).

The second method is based on the co-amplification of synthetically mutated target RNA (branched DNA [bDNA] assay [Quantiplex, Chiron Corp., Emeryville, CA, US]). The quantitative results of HCV RNA detected by both methods are reliable and reproducible. The bDNA technique is the least sensitive. After a World Health Organization (WHO) consensus meeting, a standardized international unit (IU) was established. The WHO concluded that 800.000 IU/mL was the clinically relevant threshold, whereas greater than 800.000 IU/mL was considered a high viral titer while less than 800.000 IU/mL was considered a low viral titer. The distinction is clinically relevant in regard to the likelihood of treatment response.

Genotyping

Hepatitis C virus is a single-stranded RNA virus, and is classified into at least six genotypes, each comprising of multiple subtypes, which have been distributed worldwide (5, 6). The HCV subtypes 1a and 1b are the most common genotypes in the US and these subtypes also are predominant in

Europe. The HCV genotype 3a is particularly prevalent in intravenous drug abusers in Europe and the US. The HCV genotype 4 appears to be prevalent in North Africa and the Middle East, and genotypes 5 and 6 seem to be confined to South Africa and Hong Kong, respectively (7-10).

Although the genotype of infecting virus is one of the primary predictors of response to antiviral therapy, its distribution in polytransfused thalassemic patients is still unclear throughout the world (7). In a study on thalassemia patients in Tehran-Iran, HCV genotype 1a was the most frequent (52%), followed by genotype 3a (34.5%) and genotype 1b (5 %) (11). Samimi-Rad K et al. had also determined that Iranian hemophilic patients have the same HCV genotype distribution as thalassemic patients (12). Our experience in thalassemia patients from the national data base (11) showed that HCV genotype distribution was the following: genotype 1 in 57%, 3 in 35%, 2 in 1%, and mixed in 4% . Genotype 1 was associated with a higher splenectomy rate and a greater serum ferritin. Genotype 1 is the most frequently detected HCV genotype in Iranian patients with thalassemia (11). Table 1 summarizes the HCV genotype distribution among thalassemic patients in different countries. It seems that in Lebanon, genotype 4 is predominant while in Greece, genotypes 1 and 3

Table 4.4. Distribution of HCV genotypes among thalassemic patients in different countries

Author	Country of sample origin	HCV Genotypes					
		Genotype 1 (%)	Genotype 2 (%)	Genotype 3 (%)	Genotype 4 (%)	Genotype 6 (%)	Mixed genotype (%)
Chakravarti, A (16)	India	20		36			36
Alavian SM (11)	Iran	57	1	35			4
Khaja MN (17)	India	61		36			
Ramia S (15)	Lebanon	36	5	21	37		
Wong DA (13)	Hong Kong	50				50	
Christofidou M (22)	Greece	32	10	28	30		
Sharara AI (23)	Lebanon	33	4	15	48		

have the same frequency. In Hong Kong, genotype 6 prevails in a noticeable fraction of patients (13-17). In reviews of reported prevalences of HCV genotypes from different parts of the world, it seems that genotypes 1a and 1b are more common (14, 18-21). The determination of HCV genotypes is very useful in the prediction of response to anti-viral therapies and decision making with respect to the duration of therapy.

Liver tests

The elevation of aminotransferase is not required for diagnosis. Up to 30% of patients with chronic HCV have persistently normal alanine aminotransferase (ALT). Patients with normal ALT are significantly younger and weigh less compared with those with elevated ALT, but there is no correlation to gender, race, baseline viral titer or HCV genotype (24). The degree of serum ALT elevation does not correlate well with histological severity.

Liver Histology

Liver biopsy has been the cornerstone and gold standard for the evaluation of liver damage in HCV infected patients and the management of liver diseases (25). Evaluation of the liver specimen by pathologists can show us the current status of liver injury, grade the necrotic inflammatory damage and stage the degree of liver fibrosis while also diagnosing cirrhosis and the presence of steatosis (26-28). The most important assessments in liver biopsy are the determination of grade and stage of liver injury. Another main issue in liver biopsy in thalassemia is the measurement of liver iron concentration (LIC) by atomic absorption spectrometry (29). Hepatitis C virus infection is the main risk factor for liver fibrosis in thalassemia. Adequate chelation therapy usually prevents the development of liver fibrosis in thalassemics free of HCV infection and reduces the risk of developing severe fibrosis in thalassemics with chronic hepatitis C (30).

Non-invasive tests

Liver biopsy is an invasive procedure and it is associated with pain, bleeding and perforation of other organs in some situations (31, 32). In recent

years, transient elastography (TE) was introduced as an ultrasonography technique which uses low frequency elastic waves for estimation of liver tissue, by evaluating the velocity of the propagation of the waves in the liver, in order to assess the severity of liver fibrosis (33, 34). The accuracy of the liver stiffness score is excellent for the diagnosis of cirrhosis; it is probably the most accurate noninvasive method for the early detection of cirrhosis. It is a user-friendly technique that can be performed without any preparation in less than 5 minutes in clinic or at the bedside, with immediate results and high patient acceptance. It is very likely that in future it will become the most widely used technique for the assessment of liver fibrosis (33, 35). This method is relatively new and there is few published data available regarding it in the literature. Recently, some evidence demonstrated that transient elastography can diagnose the existence of liver cirrhosis in thalassemia patients (36, 37).

Iron overload measurements

Patients with thalassemia major receive at least 0.4 mg/kg/day of heme iron, nearly 50 times the physiologic rate of iron absorption (29). Without aggressive iron chelation therapy, these patients die from endocrine and cardiac complications in their second decade of life (38). Chelation therapy is life-saving, but requires close monitoring of iron balance (39). Trends in serum ferritin are useful in tracking chelators responsiveness, are relatively inexpensive and are widely available (40). Ferritin values, however, can be confounded by inflammatory state and may give wildly inaccurate estimates of total body iron in selected patients (41). Liver biopsy can estimate the iron overload, but in patients with severe fibrosis or cirrhosis, there is a variability in iron distribution in the liver (42). Non-invasive methods for measuring liver iron overload such as magnetic resonance imaging (MRI) have been evaluated in thalassemia patients and fortunately there is a good relationship between the quantitation of liver iron concentration by biopsy and MRI signal amplitude using R2 or R2* mapping (43, 44). Heart complication still remains the leading cause of mortality. Myocardial iron deposition can occur independently of other solid organ involvement; conversely, the heart may be spared despite heavy siderosis in other tissues (45).

Conclusion remarks

• Screening of thalassemia patients for HCV infection by using anti-HCV antibody is sensitive and specific.

• For confirming the active replication of HCV, we recommend to evaluate the quantitative serum HCV RNA.

• The HCV genotyping before the start of therapy is strongly recommended.

• Measurement of liver iron concentration using liver biopsy or MRI-R2 is recommended.

• A non-invasive method such as transient elastography is preferable to liver biopsy for excluding existence of liver cirrhosis.

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Chapter 5

Treatment

Introduction

Acute hepatitis C has become relatively rare in recent years, and this is mainly due to a reduction in post-transfusion cases. However, HCV alone is responsible for 90% of acute hepatitis in poly-transfused patients and 60% to 80% of these cases develop chronic hepatitis, consequently these patients are at risk of acquiring cirrhosis and hepatocellular carcinoma (1, 2). In those patients who become acutely infected, the disease is often mild or completely asymptomatic, and it is rarely recognized outside prospective surveillance, after exposure to known risk factors, or in a surveillance system for the periodic checking of HCV infections in high risk groups, such as thalassemia patients (3). Several studies have reported on the efficacy of interferon therapy for acute HCV infections in adults. Using interferon α-2b monotherapy for 24 weeks, Jaeckel et al. showed a 98% sustained virological response in a cohort of 44 patients with an acute HCV infection (4).

The use of the newer pegylated interferons (PEG-IFN) in the treatment of adults with acute HCV has subsequently been described as producing equally excellent results (5). A single case report showed the successful treatment of acute hepatitis C with weight-based dosing of peginterferon α-2b in an eight year-old child with thalassemia major, after high viral loads had persisted for 12 weeks following the diagnosis of an acute icteric HCV infection (6).

The primary goal of therapy for chronic HCV infections is viral eradication. The efficacy of antiviral treatment of HCV is measured through the sustained virological response (SVR), which is operationally defined as the absence of HCV RNA for at least 24 weeks after the end of treatment (7, 8). Reaching SVR not only prevents advancement towards cirrhosis, HCC and liver failure, but it may also improve patients' quality of life (9, 10). Prolonged antiviral treatment with numerous complications and medical costs on the one hand and the multiplicity of factors affecting response to treatment on the other, warrant the identification of predictive variables for reaching SVR as a leading morbidity prevention factor in selected populations (11). The treatment regimen for chronic hepatitis C has changed significantly over the past decades in the antiviral treatment of HCV infections and combination therapy of peginterferon-ribavirin has become the standard around the world (1, 12).

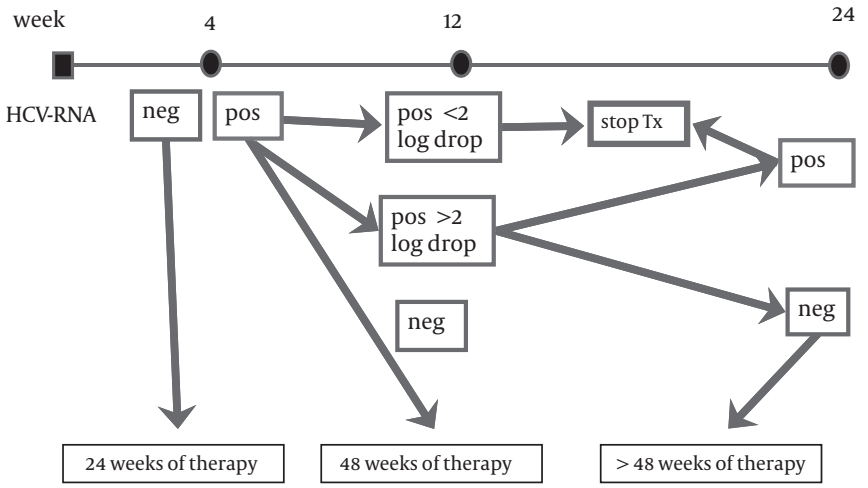
Definitions of Treatment Response

During combination treatment of chronic hepatitis C virus infection with anti-viral drugs, analysis of HCV RNA levels at specific time points has become a useful instrument for assessing treatment efficacy. The kinetics of HCV RNA during therapy is one of the most useful variables in predicting response or non-response to therapy.

A virological response in chronic HCV is defined as a reduction of HCV RNA levels in the serum (at least 2 logs) and ideally by the absence of any detectable HCV RNA by a qualitative reverse transcriptase-polymerase chain reaction (PCR) assay with a sensitivity of approximately 100 copies (50 IU) per ml. Testing should be performed early during treatment (particularly at the decision-making point at 12 weeks), at the end of treatment and six months later (13). HCV RNA quantitation at treatment

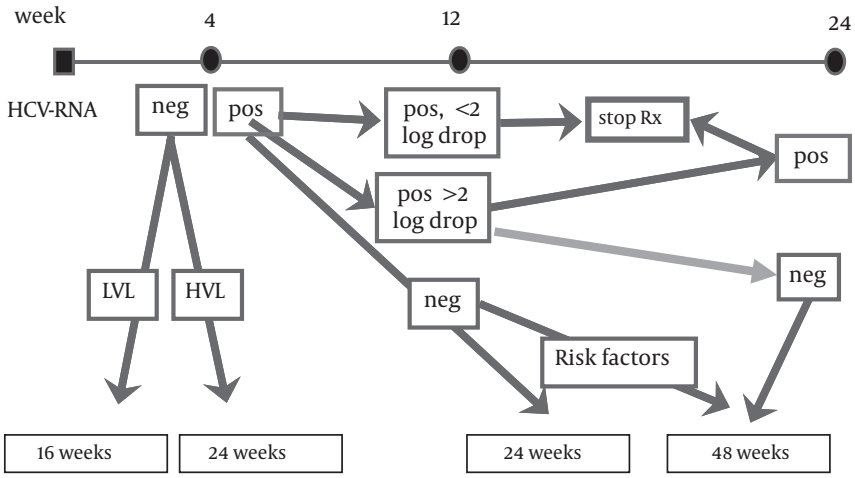
week 12 is used as a time-point to decide whether to continue or to stop treatment in genotype 1 infections (14-16). Patients with a negative HCV RNA test at week 12 of the therapy period have a high probability of achieving SVR; on the other hand, no patients with a positive serum HCV RNA after 12 weeks achieved SVR (7, 17, 18). On the evidence of many clinical trials and published guidelines (12, 19-22) the most effective duration of therapy in genotype 1 and 4 is 48 weeks and in genotype 2 or 3 it is 24 weeks (Figure 5.1) (Figure 5.2).

Figure 5.1. Response guided therapy in patients with genotype 1



If an early viral response has not been reached after 12 weeks of therapy, meaning a lack of HCV RNA level decline of >2 log from baseline or a negative qualitative test (<50 IU/ml), treatment is generally stopped. These patients have only a small likelihood of achieving SVR after 48 weeks of treatment. Recently, a negative HCV RNA treatment response in week four, rapid viral response (RVR), has been used to decide whether a shorter-than-standard treatment course can be used or not, particularly in those patients with genotype 1 infections who have low baseline viral loads (<600 000 IU/ml) (23). This also seems to be valid for patients infected with genotype 2 or 3, for the latter in those with a low baseline viral load (<600 000 IU/ml), for whom a rapid viral response indicates that a shorter-than-standard

Figure 5.2. Response guided therapy in patients with genotype 2/3



treatment (12–16 weeks) can be used with reasonably preserved SVR (24-28). Sustained viral response rates are defined by the absence of detectable HCV RNA in the serum by a sensitive (qualitative) PCR assay six months after completion of treatment. Relapse can occur following an end-of-treatment response, which is indicated by a recurrence of detectable HCV RNA (and often ALT elevation) after discontinuing therapy. Non-response can be defined as the continued presence of HCV RNA at the end of treatment, the reappearance of HCV RNA after end virological response (EVR) (breakthrough), or failure to achieve a 2-log reduction of viral load at 12 weeks. In a virological sense, it includes partial and absolute non-response, but the implications of these fine distinctions for prognosis and retreatment, are not yet clear (13).

Slow virological responders who had positive HCV RNA at 12 weeks of therapy, but were negative at 24 weeks of therapy, and received the 72-week therapy, had a significantly higher probability of achieving SVR than their counterparts who received only the 48-week therapy [RR = 1.44 (95% CI, 1.20-1.73)]. This meta-analysis showed that the 72-week therapy with peginterferon and ribavirin is significantly superior to the standard 48-week therapy in slow responders with a HCV genotype 1 infection (29) (Figure 5.1).

The COBAS Amplicor Monitor with a lower detection limit of <600 IU/ml was earlier used frequently as a HCV RNA quantitative test, however, this has recently been substituted with the COBAS TaqMan test with a lower detection limit of <15 IU/ml (30).

Counseling

There have been conflicting reports about the sexual transmission of HCV infections. The detection of anti-HCV positivity ranged from 0% to 5% in monogamous partners of transfusion-associated hepatitis patients (31-33). A possible explanation is that sexual transmission occurs only in association with specific HCV genotypes or in the presence of specific mutations along the HCV genome. The risk of HCV transmission in non-sexual household members of thalassemia patients is possible, but it is very low (34, 35). We should not forget that there are some reports in household contacts of thalassemia patients with HCV, high prevalence of HCV infections for example from Pakistan and India (36, 37). It is clear that the high prevalence is related to higher contact with other risk factors in their communities, or it may be related to sharing shaving equipment which is a common source of infection (38).

Management of HCV infections in thalassemia patients needs a multidisciplinary team involving a hematologist, hepatologist, cardiologist, psychologist, and endocrinologist. Consultation with a psychiatrist for evaluation of the existence of depression and management of it before therapy and an eye consultation for a retina examination before the start of antiviral drug therapy are necessary. Thalassemia patients have cardiomyopathy and they should be carefully evaluated before the start of therapy and sometimes after therapy as well. Patients with severe, uncontrolled cardiomyopathy should be excluded from anti-viral therapy.

General measures

According to our data, strict iron chelation to decrease serum and liver iron content before and during ribavirin therapy of thalassemia patients is strongly advised. The decision on the treatment and monitoring of thalassemia major patients should be carefully individualized according to any

other conditions that accompany patients' underlying hemoglobinopathy. Moreover, by close observation and frequent transfusion, the rate of severe hemoglobin drop can be minimized, as maintaining hemoglobin levels above 8-9 g/dl is necessary. High iron content in the serum and liver with its probable role in conferring patients' interferon resistance and its synergistic effect on the progression of liver fibrosis is another major confounder in the treatment of thalassemia major patients. Increased hepatic iron deposition has been shown to correlate with the severity of hepatic inflammation and fibrosis in patients with chronic hepatitis C, and impair responses to IFN-based therapy (39, 40). Some studies have suggested that iron depletion is an adjuvant to antiviral therapy in chronic HCV infections and showed that iron removal and dietary iron restriction could improve the rate of response to IFN (41, 42). Proper management of hepatic siderosis before the initiation of HCV therapy in thalassemia patients is therefore essential. Thalassemia major patients have high iron stores and the proper removal of iron with chelating drugs is not always successful, or it may not be properly implemented in all situations (43). Concerning chelation treatment, while deferiprone may increase the risk of neutropenia, no findings on the safety of deferasirox in association with combined antiviral treatment have so far been reported in the literature. Therefore, switching to deferoxamine treatment during antiviral treatment for hepatitis C can be recommended (44).

Antiviral therapy

Treatment of HCV in thalassemia patients aims to eradicate the virus, facilitate improvements in liver damage, avoid fibrosis progression, decrease the risk of hepatocellular carcinoma, improve health-related quality of life and patients' survival (43). Unfortunately, there is a deficit of data regarding the management of this special group and most clinical trials exclude this group from studies (45). Chronic hepatitis C (CHC) is a major cause of morbidity and mortality in thalassemia major patients, particularly in those who had received their first transfusion before the introduction of the HCV donor screening program. Interferon alpha is the backbone of treatment for chronic HCV, it is a glycoprotein that has direct antiviral mechanisms and it also has processes for the enhancement of immune responses to the virus.

IFN Monotherapy

Monotherapy with interferon at three million units, three times a week for 48 weeks produces low sustained virological response rates of less than 20% (46-50). In reported studies using alpha interferon monotherapy with three million units, three times per week, for a duration of 24-48 weeks (regime used in most studies) in thalassemia the response rate differs from 20% to 50%, which depends on the genotype and other variables (51-60). The presence of cirrhosis, high iron concentrations in the liver tissue and genotype 1b are the main clinical and virological characteristics which predict a poor response to therapy (7, 17, 18).

Pegylated interferons have a covalently attached polyethylene glycol moiety that results in more sustained absorption and reduced clearance. This has allowed a once weekly dose, compared with the three times weekly dose required for standard interferon. The safety profile is similar to standard interferon. There is little data regarding the use of pegylated interferon alone in thalassemia patients infected with HCV infection in the literature.

The first report was done by Mirmomen et al. in Iran as a multicenter study using Pegasys 180 microgram once per week for one year. In total, 32 subjects, 18 to 42 years-of-age received the therapy and the SVR was 60.8% (61). This very high response rate was remarkable in the thalassemia patients and therefore the question is. Why was the SVR rate in Iranian thalassemia patients higher than expected? After six years we found that Iranian HCV infected patients had a favorable IL-28 B polymorphism that increased the SVR in the study population (61-64).

Inati et al. (65) administered 180 microgram of Pegasys weekly, for 12 months, in 12 thalassemia HCV-infected patients, and 33% (4 out 12) achieved SVR. The patients tolerated the drug very well and being younger than 18 years was an important variable in the prediction of SVR (65). Kamal et al. (66) reported a 46% SVR by using Pegasys 180 microgram weekly, for 12 months, in 39 thalassemia HCV infected patients in 2006. Kountouras et al. (67) reported a SVR of 13% by using pegylated alpha interferon 2b (PegIntron), 1.5 microgram/kilogram/week, for 48 weeks in thalassemia HCV infected patients (67). The study group had a 24% dropout rate and in 19% of patients the rate of transfusion was increased.

Combination with Ribavirin

The treatment of chronic HCV infection has improved significantly over the past several years with combination PEG IFN and ribavirin therapy. SVR is achievable in nearly half of the patients with genotype 1 and about 80% of those with genotypes 2 and 3 (14, 68, 69). In view of the high cost and the significant side effects of this combination therapy, it is important to identify patients who are most likely to benefit from it before starting treatment (70). SVR in the real world is different from clinical trials reports and we should judge each case separately. Although combination therapy of pegylated interferon and ribavirin significantly increases SVR and increases the probability of reaching SVR by 50% (71), the degree of response depends on a variety of factors and these may differ in diverse patient populations (71). Viral genotype, viral load, patient age, BMI, race, environment and several other factors have been shown to correlate with SVR (7, 72, 73).

In patients without hemoglobinopathies, current guidelines strongly recommend a combination therapy of ribavirin, and either peginterferon alfa-2a or 2b. This combination therapy can yield a SVR rate of more than 50% in genotype 1 and a 70-80% SVR in genotype 2 and 3 infected patients (6-10). In contrast, in patients without inherent hemoglobinopathy, ribavirin which is one of the major determinants of SVR can induce life-threatening anemia in thalassemia major patients, and thus, it is generally considered contraindicated in these patients (11, 12). Currently, IFN without ribavirin is widely approved as a first-line therapy for chronic HCV infection in transfusion-dependent thalassemia patients. The introduction of combination therapy with interferon alpha, injected subcutaneously three times per week, and daily oral ribavirin is a major advance (74), but the main problem with thalassemia is the exacerbation of anemia after the use of ribavirin. We thus have a double edged sword, if we use interferon as a monotherapy we will have a low response rate, and if we use ribavirin we will have more requests for blood transfusions.

As mentioned above, the main limitations in the treatment of HCV infections in thalassemia patients relate to ribavirin use. Consensus statements have listed anemia as an absolute contraindication to ribavirin in hepatitis C, because of the tendency of ribavirin and its metabolites to accumulate within the erythrocytes, leading to oxidative damage of red blood cell mem-

branes and hemolysis (75). Because of potential hematologic adverse events ribavirin is, however, reserved for IFN non-responders or for use in experimental situations (45). In fact, ribavirin can increase SVR in thalassemia patients with a HCV infection and it can be well tolerated, but due to the induction of hemolysis the need for blood transfusions increases 30-60%, and it also leads to an increase in iron overload. More recently, trials comparing peginterferon monotherapy and the combination of peginterferon and ribavirin have shown a considerable increase in SVR rates in the dual therapy arm, albeit at the cost of a modest increase in transfusion requirements. In fact, SVR rates in these relatively small trials were comparable to treatment in experienced patients without thalassemia or hepatic iron overload (43, 65, 76-83).

In the largest study in the world, conducted in Iran on 280 thalassemia patients (76), Tabatabaei et al. compared the monotherapy group (pegylated interferon alpha 2-a 180 microgram/weekly) with a combination group (pegylated interferon alpha 2-a 180 micrograms plus ribavirin). Baseline characteristics of the studied patients are in (table 5.1). As presented in Table 1 most of the major predictors of virological response including HCV RNA level, sex, weight, BMI, HCV type, age and liver histological findings, appeared to be similar in both groups.

Table 5.1. Baseline Characteristics of Studied Patients

Patients Characteristics	Group (A)	Group (B)	P
No. of patients	199	81	
Sex			
Male/Female M (%)	123/76 (62%)	42/39 (60%)	0.1
Mean Age	24±5.5	25±7.2	0.3
range	11-43	12-54	
BMI	20.4±0.2	20.2±0.2	
range	14-28	15-25	
ALT (U/L)	91±56	79±60	0.06
Range Normal (<40 U/L), n (%) Elevated, n (%)	12-994 35 (18%) 164 (82%)	15-338 24 (30%) 57 (70%)	0.02
AST (U/L)	77±61	64±41	0.08
Range	17-638	13-206	
Normal (<40 U/L), n (%)	43 (22%)	29 (36%)	0.01
Elevated, n (%)	156 (78%)	62 (64%)	

Hb	10±1.5	9.5±1.3	0.4
HCV viral load (IU/mL)	800000±11000	799000±88000	
range	2000-8000000	7540-4090000	
Log10 Serum HCV Viral Load (IU/mL)	5.5±0.7	5.5±0.6	0.5
>6 (copy/ml), n (%)	85 (43%)	31 (38%)	
Serum ferritin (ng/mL)	2130±1777	1710±1498	0.06
range	210-8132	300-6650	
History of Splenectomy			
Yes/No Y (%)	135/64 (68%)	49/32 (60%)	0.2
HCV Type			
Genotype 1, n (%)	119 (60%)	41 (51%)	0.1
Genotype 2, n (%)	1 (0.5%)	2 (2.5%)	
Genotype 3, n (%)	65 (33%)	33 (41%)	
Mixed infection, n (%)	10 (5%)	2 (2.5%)	
Untypable, n (%)	4 (2%)	3 (4%)	
Stage of liver fibrosis	3.2±1.6	3.3±1.4	0.5
0-2, n (%)	50 (31%)	16 (20%)	0.3
3-4, n (%)	69 (43%)	37 (53%)	
5-6, n (%)	41 (26%)	17 (24%)	
Grade of liver inflammation	6.3±0.2	6.3±0.4	0.9
0-6, n (%)	92 (59%)	43 (63%)	0.7
7-12, n (%)	58 (37%)	23 (34%)	
13-18, n (%)	7 (4.5%)	2 (3%)	
Stage of Liver Sidrosis	3±1	2.9±1	
0-2	37 (19%)	16 (20%)	0.2
3-4	118 (59%)	34 (42%)	
Previous treatment	136 (68%)	38 (47%)	0.001
Naïve	61 (31%)	43 (53%)	0.0006
Standard IFN	62 (31%)	24 (30%)	0.8
Standard IFN+RVB	74 (37%)	14 (17%)	0.001

*Plus–minus values indicate means ±SD. except for liver enzymes and serum ferritin there were no significant differences among the two treatment groups with regard to baseline characteristics. ALT denotes alanine aminotransferase, AST aspartat aminotransferase , Hb hemoglobin and HCV hepatitis C virus.

*Hepatitis C virus level was determined with the use of the amplicor assay version II (Roche), for which the lower limit of quantitation is 50 IU per milliliter.

*Percutaneous liver-biopsy specimens obtained before treatment were evaluated according to modified knodell score scaling system. The modified knodell scoring system classifies fibrosis according to a 6-point scale: 0, no fibrosis; 1, Fibrous expansion of some portal areas; 2, Fibrous expansion of most portal areas; 3, Fibrous expansion of most portal areas with occasional portal to portal bridging; 4, Fibrous expansion of portal areas with marked bridging of portal to portal as well as portal to central; 5, Marked bridging with occasional nodules; 6, Cirrhosis.

Ref: Tabatabaei SV, Alavian SM, Keshvari M, Behnava B, Miri SM, Karimi Elizee P, et al. Low dose ribavirin for treatment of hepatitis C virus infected thalassemia major patients; new indications for combination therapy. Hepat Mon. 2012;12(6):372-81 with permission

Our primary efficacy analysis showed that the SVR rate was significantly higher in group (A) patients who received the combination therapy with low dose ribavirin in comparison with patients of group (B) who received monotherapy. Furthermore, multiple logistic-regression analysis with adjustment for baseline characteristics revealed that low dose ribavirin was an even stronger independent predictor of a SVR than had been shown in our primary analysis. Sustained virological response (SVR) was significantly higher in patients who received ribavirin (51% vs. 38% P = 0.02). In a multivariate regression, an OR of ribavirin for the prediction of SVR was 2.2 (95% CI 1.24-3.91). The SVR was significantly higher in the ribavirin group in subgroups of patients older than 24 years-of-age, elevated ALT, ferritin < 2006 ng/mL, previous treatment failure, genotype 1, positive history of splenectomy, fibrosis score of 0-4 HAI and viral load < 600 000 IU/mL. Treatment discontinuation due to safety concerns were comparable between the treatment groups (6.5% and 8%). Furthermore, transfusion intervals were almost halved in patients who received low dose ribavirin. These findings are consistent with the results of previous studies (7, 84, 85). Although in non-thalassemia patients, higher liver and serum iron content have been shown to undermine the virological response to anti-HCV therapy, no study except for one case report, has reported this phenomenon among thalassemia patients (45, 84-88). Serum ferritin and a liver pearl score did not reach significance level for predicting SVR among the total studied population in the present investigation. Nonetheless, our subgroup analysis showed that patients with serum ferritin levels below 2006 ng/mL responded to ribavirin significantly more positively than those with a lower level of serum ferritin. Relapse rates were 23% for combination therapy and 35% for monotherapy (P=0.01). In a multivariate binary logistic regression we found that; being female, age below 24 years, and non-1 genotype, were independently associated with SVR, conversely; age over 24, genotype-1 and not receiving ribavirin, were significant predictors of relapse.

Other factors related to treatment such as; the necessity of peginterferon dose reduction, discontinuation of treatment, and compliance with therapy, were similar in both treatment arms. More patients discontinued their treatments owing to an insufficient therapeutic response in group (A), rather than group (B). The higher rate of previous treatment failure in

group (A), even with ribavirin, could be a possible reason for this finding. The safety profile was similar among these two groups; treatment discontinuations due to adverse events were observed in 6.5% to 8.6% of patients, respectively. However, the transfusion interval was almost halved in the patients who had received ribavirin (Table 5.2).

This large prospective study showed that low dose ribavirin in chronically HCV infected thalassemia patients is safe, tolerable and effective. Accord-

Table 5.2. Adverse Events in The Study Patients

Adverse events	Group (A)		Group (B)	
	N	Percent	N	Percent
Death	3	1.5%	5	6%
Non-response	21	10%	5	6%
Dose Reduction	39	19%	15	18%
Neutropenia	33	16%	11	13%
Thrombocytopenia	6	3%	4	5%
Headache	46	23%	20	25%
Lethargy	41	21%	11	12%
Dizziness	23	12%	8	10%
Insomnia	34	17%	12	15%
Irritability	67	34%	23	28%
Depression	15	7%	10	12%
Fatigue	60	30%	19	23%
Weight loss	12	6%	3	3.7%
Flue like syndrome	11	5%	5	6%
Myalgia	65	33%	26	32%
Arthralgia	59	30%	23	28%
Nausea	11	5%	4	5%
Diarrhea	13	6%	4	5%
Cough	19	9%	9	11%
Alopecia	85	43%	33	41%
Dry skin	26	13%	21	26%
Pruritis	19	9%	3	4%
Rash	5	2%	3	4%
Chills	23	12%	13	16%
Fever	48	24%	23	28%

Ref: Tabatabaei SV, Alavian SM, Keshvari M, Behnava B, Miri SM, Karimi Elizee P, et al. Low dose ribavirin for treatment of hepatitis C virus infected thalassemia major patients; new indications for combination therapy. Hepat Mon. 2012;12(6):372-81 with permission

ing to the present study, adult thalassemia patients with HCV infections can be treated successfully with low dose ribavirin. Hence, we strongly advise combination therapy in thalassemia patients with the aforementioned clinical characteristics. On the other hand, ribavirin does not seem to be beneficial in thalassemia patients below 18 years-of-age (76).

The major impact of low dose ribavirin was found in thalassemia major patients who were; older than 24 years, had low serum ferritin (<2006 ng/mL), previous treatment failure, elevated ALT, liver fibrosis of 0-4 HAI, history of splenectomy, viral load ≤ 600 000 IU/mL, and HCV genotype 1.

In a meta-analysis of the literature concerning the treatment of chronic hepatitis C in polytransfused thalassemic patients, we have demonstrated that thalassemic patients with a genotype 1 infection benefited significantly from the addition of ribavirin to their therapeutic regimen (8). Table 1 shows the summery of the literature on the treatment of HCV in thalassemia is presented in Table 2.

This meta-analysis (Table 5.3 - 5.4) showed that thalassemia patients with a genotype 1 infection improved notably with the addition of ribavirin to their therapeutic regimen with a doubling of SVR rates, from 30% to 61%, similar to non-thalassemia patients (45) (Tables 5.5 - 5.6). It seems that the addition of ribavirin to IFN increases the SVR rate in genotype 1-infected subjects more than in non-genotype 1-infected thalassemic individuals. Rate of SVR. Using ribavirin in thalassemia patients increases transfusion needs by a median of 30–40%, but it does not increase major adverse events or treatment withdrawal (8, 76) (Figures 5.3 - 5.4). Based on the above evidence, I would like to emphasize the benefits achieved through the addition of ribavirin to peginterferon in thalassemia patients with a HCV infection. This combination is relatively safe and effective and should be considered particularly in the expert management of hematologic disorders setting (Table 5.7).

Despite improvements in treatments for HCV infection, not all patients are cured with anti-viral therapy. Patients, who have contraindications to antiviral therapy or have failed previous cycles of antiviral therapy, should be monitored regularly. This monitoring is even more important in patients with severe fibrosis of the liver or who are cirrhotic. This needs to in-

Table 5.3. Summary of the literature data: studies and patients' characteristics

Study Characteristics						Patients Characteristics						
Author		Study design	Sample Size	Publication year	Country of sample's origin	Sex (% m)	Age y	Genotype 1 and 4	Serum ferritin (µg/l)	Liver iron content	HCV viral load Copy/ml	Stage of fibrosis	ALT IU/ml
1	Di Marco, (16) 42	Prosp	12	1992	Italy	46%	13	ND	2490	ND	ND	ND	294
2	Donohue, (21) 144	Prosp	12	1993	UK	60%	20	ND	2917	ND	ND	2.2	221
3	Clemente, M. G. (24) 33	CT	51 T 14 C	1994	Italy	ND	14	ND	2195	19* µg/gm	ND	ND	261
4	Telfer, P. T. (32) 133	Prosp	11	1997	UK	ND	27	45%	2967	10 µg/mg	22×106	ND	116
5	Di Marco (33) 134	Prosp	70	1997	Italy	47%	14	58%	3241	72 µg/g	ND	ND	111
6	Spiliopoulou, I. (27) 105	Prosp	13	1999	Greece	38%	14	69%	ND	ND	0.2×106	2.6	129
7	Pizzarelli, G (15) 206	CT	38 T 13 T 28C	1999	Italy	57% 53%	14 17	100% 100%	3946 4234	12* 12*µg/dL	ND	ND	195 186
8	Sievert, W. (26) 101	Prosp	28	2002	Australia	60%	26	42%	1026	2808 µg/g	1.6×106	1.5	105
9	Li, C. K. (31) 132	Prosp	18	2002	China	50%	16	77%	2142	5.4 mg/g	ND	ND	ND
10	Mirmomen (36) 75	Prosp	29	2003	Iran	ND	25	ND	ND	ND	ND	ND	ND
11	Mirmomen (25) 74	Prosp	32	2004	Iran	59%	24	46%	1712	ND	ND	3.7	92
12	Artan, R (28) 123	Prosp	10	2005	Turkey	50%	17	ND	2959	ND	ND	ND	93
13	Inati, A. (29) 124	RCT	12 T 8 T	2005	Lebanon	73% 75%	22 16	100%	1763 2757	8 mg/g 8.2	0.3×106 0.4×106	ND	86 103
14	Syriopoulou, V. (30) 126	Prosp	89	2005	Italy	52%	20	14%	3192	ND	ND	2.9	190
15	Kountouras, D (35) 197	Prosp	37	2007	Spain	43%	34	65%	2295	ND	ND	ND	106
16	Harmatz, P (34) 185	Prosp	21	2008	USA	ND	33	57%	1541	5.8	ND	2	74

Ref: Alavian SM, Tabatabaei SV. Treatment of chronic hepatitis C in polytransfused thalassaemic patients: a meta-analysis. J Viral Hepat. 2010;17(4):236-44 with permission

Table 5.4. Summary of the literature data: characteristics of treatment and response

Author		Treatment characteristics					Sustained viral response	End of treatment response	Dropout rate
		protocol	IFN doses	RBV doses (mg/day)	Duration w	Interferon total dose			
1	Clemente, M. G. (24) 33	IFNα2b	3		60	540	37%	41%	0%
2	Di Marco,* (16) 42	IFNα2b	5+3		8+18	282	ND	ND	47%
3	Sievert, W. (26) 101	IFNα2b	3		24	216	28%	28%	7%
4	Spiliopoulou, I. (27) 105	IFNα2b	3		72	648	76%	100%	15%
5	Artan, R (28) 123	IFNα2a	5		24-48	720	80%	ND	0%
6	Syriopoulou, V. (30) 126	IFNα2a	3		48	432	52%	55%	4%
7	Di Marco (33) 134	IFNα2b	5+3		8+40	480	40%	40%	4%
8	Donohue,* (21) 144	IFNα2b	3		24	216	ND	ND	0%
9	Pizzarelli, *G (15) 206	IFNα2a IFNα2b	5+3 3		24+24 48	576 432	ND	ND 47%	0%
10	Mirmomen (36) 75	IFNα2b	3		48	432	31%	52%	7%
11	Mirmomen (25) 74	PEGα2b	180		48	8640	43%	81%	6%
12	Kountouras, D (35) 197	PEGα2b	1.5 μg/kg/wk		48	4320*	13%	27%	24%
13	Inati, A. (29) 124	PEGα2b+RVB PEGα2b+PLC	180	6-10 mg/kg	48	8640	62% 33%	75% 41%	0%
14	Li, C. K. (31) 132	IFNα2b+RVB	3	16 mg/kg	48	432	72%	72%	0%
15	Telfer, P. T. (32) 133	IFNα2b+RVB	3	1000	24	216	45%	63%	0%
16	Harmatz, P (34) 185	PEGα2a+RVB	180	800-1200*	24-48	8640	33%	ND	23%

*excluded from meta-analysis because SVR was not reported

Ref: Alavian SM, Tabatabaei SV. Treatment of chronic hepatitis C in polytransfused thalassaemic patients: a meta-analysis. J Viral Hepat. 2010;17(4):236-44 with permission

Table 5.5. rate of sustain viral response in genotype 1 infected thalassemic subjects reported in six trials

Author	Mode of therapy	Responders	Non-responders
		Genotype 1, % (n/N)	Genotype 1, % (n/N)
Sievert, W. (26) 101	Mono	37.5 (3/8)	47.3 (9/19)
Syriopoulou, V. (30) 126	Mono	37.5 (6/16)	36.8 (7/19)
Di Marco (33) 134	Mono	39 (11/28)	71.4 (30/42)
Li, C. K. (31) 132	Combination	76.9 (10/13)	80 (4/5)
Telfer, P. T. (32) 133	Combination	50 (2/4)	42.8 (3/7)
Harmatz, P (34) 185	Combination	75 (6/8)	50 (6/12)

Ref: Alavian SM, Tabatabaei SV. Treatment of chronic hepatitis C in polytransfused thalassaemic patients: a meta-analysis. J Viral Hepat. 2010;17(4):236-44 with permission

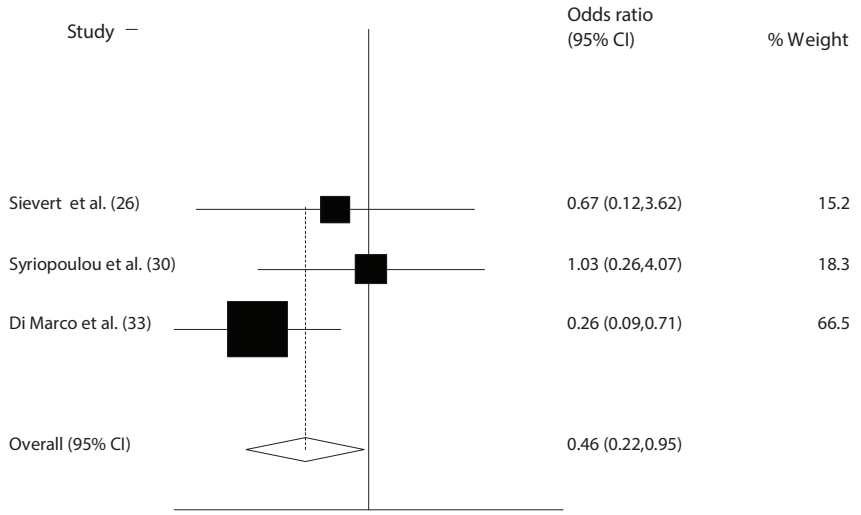
Table 5.6. Rates of sustained viral response in subgroups of patients stratified according therapeutic agents and genotypes

Subgroup of patients	No. of patients	Rate of sustained viral response (95% CI)	Heterogeneity assessment		
			Q (df)	I2	P value
Genotype 1 (overall)	97	42.2% (26.6-57.8)	10.672 (5)	53.1%	0.058
Genotype 1 who received standard IFN monotherapy	66	29.5% (18.7-40.4)	1.724 (2)	0%	0.422
Genotype 1 who received combination therapy of standard IFN plus ribavirin	31	60.9% (32.4-89.4)	1.533 (1)	53.3%	0.216
Non-genotype 1 (overall)	84	48.6% (38.3-59)	5.702 (5)	12.3%	0.336
Non-genotype 1 who received standard IFN monotherapy	66	51.9% (39.9-63.9)	0.888 (2)	0%	0.642
Non-genotype 1 who received combination therapy of standard IFN plus ribavirin	18	51.5% (23.3- 79.6)	2.107 (1)	52.5%	0.147
PEG-IFN monotherapy	77	28.4% (17.2-52.8)	8.838 (2)	77.3%	0.012
PEG-IFN plus ribavirin combination therapy	33	43.6% (29.4-57.8)	2.80 (2)	28.5%	0.247
Standard IFN monotherapy	277	46.9% (35.1-58.7)	25.027 (6)	76%	<0.0001
Standard IFN plus ribavirin combination therapy	29	63% (46.1-80)	2.163 (1)	53.7%	0.141
Ribavirin combination therapy	62	52.9% (33.7-72.2)	7.71 (3)	74%	0.052

P<0.100 considered significant for heterogeneity assessment; df, degree of freedom calculated by number of trials minus 1

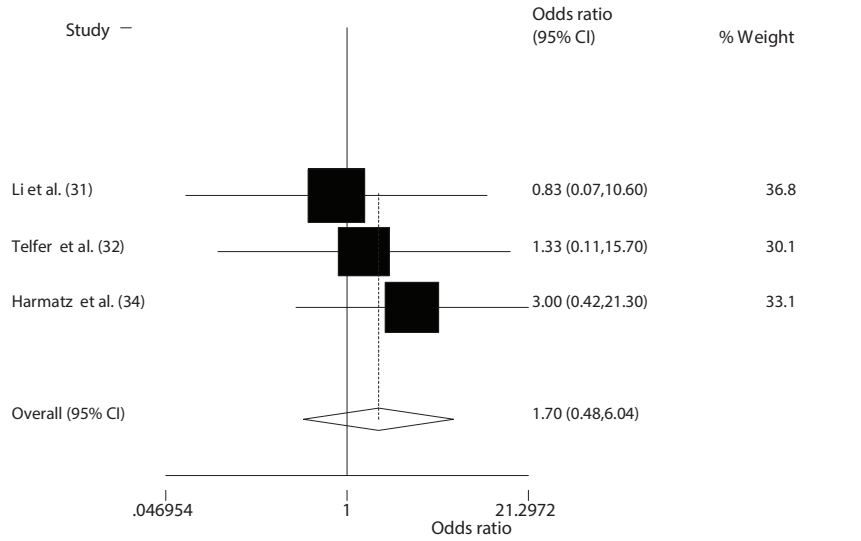
Ref: Alavian SM, Tabatabaei SV. Treatment of chronic hepatitis C in polytransfused thalassaemic patients: a meta-analysis. J Viral Hepat. 2010;17(4):236-44 with permission

Figure 5.3. Pooled odd ratio of SVR rate in genotype 1 vs non-genotype 1 infected thalassemic patients with IFN monotherapy



Ref: Alavian SM, Tabatabaei SV. Treatment of chronic hepatitis C in polytransfused thalassaemic patients: a meta-analysis. J Viral Hepat. 2010;17(4):236-44 with permission

Figure 5.4. Pooled odd ratio of SVR rate in genotype 1 vs non-genotype 1 infected thalassemic patients with ribavirin combination therapy



Ref: Alavian SM, Tabatabaei SV. Treatment of chronic hepatitis C in polytransfused thalassaemic patients: a meta-analysis. J Viral Hepat. 2010;17(4):236-44 with permission

Table 5.7. side effects and cause of withdrawal reported by authors

Author		Side effects	Dropout cause
1	Clemente, M. G. (24)	Granulocytopenia (n=6) fever, fatigue, anorexia and thrombocytopenia were frequent	
2	Di Marco, (16)	ND	persisting fever (n=1) Hyperhemolysis (n=2)
3	Sievert, W. (26)	ND	Death (n=1) ND (n=1)
4	Spiliopoulou, I. (27)	Fever (n=4), weight loss (n=5), anorexia (n=2) headache, myalgia, arthralgia, neutropenia and thrombocytopenia (n=0)	Weight loss (n=1)
5	Artan, R (28)	ND	
6	Syriopoulou, V. (30)	ND	Death (n=4)
7	Di Marco (33)	Mild flu-like syndrome (n=70) Hyperhemolysis (n=1)	persistent flu-like symptoms (n=2)
8	Donohue, (21)	Mild neutropenia (n=7) severe Neutropenia (n=3)	
9	Pizzarelli, G (15)	Cutaneous reaction to DFX (n=5) Coomb's positive hemolytic Anemia (n=1), neutropenia (n=2), thrombocytopenia (n=4)	
10	Mirmomen (36)	Flu syndrome (n=29), chills or fever (n=14), local pain (n=14), transient gastrointestinal symptoms in (n=13), weakness (n=5), local induration (n= 3) and edema (n=2)	illegal concurrent medication usage (n=1) hypothyroidism (n=1)

11	Mirmomen (25)	Weight loss (n=10), alopecia (n=15), flue like syndrome (n=31), fever (n=9), leucopenia (n=5), anorexia (n=10), local injection pain (n=10), thrombocytopenia (n=4)	Death (n=1)
12	Kountouras, D (35)	increased Transfusion requirements (n=7) others ND	increased transfusion rate (n=9) arrhythmia (n=1) , EBV pericarditis (n=1) , allergy (n=1) , leucopenia (n=2), thrombocytopenia (n=1)
13	Inati, A. (29)	increased Transfusion requirements (n=12), leucopenia (n=1)	
14	Li, C. K. (31)	fever, chills, anorexia and malaise were common 30% increased in the annual blood consumption during treatment	
15	Telfer, P. T. (32)	Mild neutropenia (n=3) 41% increased in transfusion during treatment	
16	Harmatz, P (34)	Neutropenia (n=11), Flu-like symptoms (n=11), Headache (n=11), fatigue (n=10), nausea (n=9), Weight loss (n=2), Irritability (n=4), Abdominal pain (n=6), Insomnia (n=7), Alopecia (n=2), Anxiety (n=2),	Death (n=1) persistent cough (n=1) extreme fatigue (n=1) pregnant spouse (n=1)

Ref: Alavian SM, Tabatabaei SV. Treatment of chronic hepatitis C in polytransfused thalassaemic patients: a meta-analysis. J Viral Hepat. 2010;17(4):236-44 with permission

clude; biochemical parameters, ultrasound analysis of the liver structure, and transient elastography (Fibroscan), if available, every 6-12 months to follow the evolution from chronic hepatitis to cirrhosis and to monitor patients with cirrhosis for HCC (44).

Management of Side Effects

Numerous side effects have been reported to occur with anti-viral therapy. The major types of side effects include; influenza-like symptoms such as fever and chills, gastrointestinal disturbances, psychiatric symptoms such as depression, insomnia, lack of concentration, hematologic abnormalities (leucopenia, neutropenia, and thrombocytopenia), thyroid dysfunction, and occasionally respiratory and dermatologic symptoms such as hair loss, dry skin, and skin rashes (89). These side effects may be treatment limiting and require dose reduction or drug discontinuation (90-92). Pegylated interferons have significantly improved pharmacokinetics, resulting in improved antiviral efficacy, and they also have the potential to alter the side effect profile (93, 94). Most side effects are mild and reversible and are amenable to control, however, some of them are severe and can even be life threatening. Premature withdrawal from therapy due to laboratory abnormalities or adverse events has occurred in at least 15% of patients and dose reduction in 20-30% combination therapy patients (14, 90, 92, 94, 95). Injection site reactions and injection site inflammation are particularly common, but they are generally mild and rarely dose limiting (68). Numerous case reports of serious adverse events, although infrequent, may occur with therapy and cause significant morbidity and end-organ damage. A partial list includes; acute psychosis, suicidal ideation or attempt, confusion and coma, personality changes, memory loss, retinopathy, retinal hemorrhage, visual loss, neuropathy, tinnitus, hearing loss, photosensitivity, severe skin rash, cardiac arrhythmias, congestive heart failure, interstitial pneumonitis, acute renal failure, bacterial infections (particularly in patients with cirrhosis and thalassemia), and induction or exacerbation of autoimmune diseases (type 1 diabetes mellitus, celiac disease, thrombocytopenic purpura, myasthenia gravis, and lupus-like syndrome) (96-106).

Neutrophil counts decrease within the first two weeks of therapy initiation and usually stabilize over the next four weeks (14, 68, 94). Neutrophil

counts rapidly return to baseline after therapy is discontinued. Dose reduction of peginterferon alpha-2b is recommended when neutrophil counts are lower than 759 cells/mm, this appears to be based on empiric evidence extrapolated from patients undergoing cancer chemotherapy, and the administration of granulocyte colony stimulating factor should be advised. Decreases in platelet counts occur with therapy, but they have been associated infrequently with dose reduction or discontinuation.

The tendency to exacerbate diabetes mellitus, infection and septicemia, should be considered in patients on anti-viral therapy and they should be diagnosed early for better control and to reach SVR. Significant ocular complications such as an irreversible decrease in visual acuity may develop in patients treated with pegylated interferon. The most important risk factor for developing retinopathy is hypertension. The high rate of retinopathy in patients with hypertension and diabetes mellitus suggests that patients should be carefully monitored (107).

Adherence to therapy appears to influence sustained viral response rates. Adherence is a complex human behavior, therefore, the issue of adherence should be attended to in any protocol as the management of side effects can increase patients' adherence rates. This indicates the need for more research on the management of side effects related to both interferon and ribavirin. Improving compliance with therapy through measures such as; patient education, close follow-up, adequate treatment of side effects, and minimization of dose changes may increase the efficacy of treatment (90).

IL28B Polymorphism

Different sustained virological response (SVR) rates in various populations is a challenging fact that has been observed by researchers and inspired them to search for causes (64). In September 2009, Ge et al. (108) in a genome-wide association study (GWAS) found the rs12979860 single nucleotide polymorphism (SNP), which is located three kb upstream of the IL28B gene, to be the strongest host genetic predictor of SVR in hepatitis C genotype 1. They observed that rs12979860 CC patients, regardless of their ethnicity, reach SVR rates approximately twice as often as rs12979860 TT patients. Our experience showed that Iranian, and especially the thalas-

semia patients, responded better to anti-viral therapy in comparison with the literature (62, 63, 109).

Concluding Remarks

• We should give assurances to thalassemia patients with HCV infections and their household contacts regarding the low risk of transmission in the family. However, they should consider health precautions regarding not sharing personal equipment in the family.

• Adult thalassemia patients with a HCV infection can be treated successfully with low dose ribavirin. Hence, we strongly advise combination therapy in thalassemia patients with the aforementioned clinical characteristics.

• However, ribavirin does not seem to be beneficial in thalassemia patients below 18 years. Please treat them early!

• When using ribavirin in thalassemia patients, transfusion needs increase by a median of 30–40%, thus it is important to maintain hemoglobin levels above 8- 9 g/dl

• Using suitable iron chelators for the control of iron over load is recommended.

• The duration of therapy in genotype 1 and 4 is 48 weeks and for genotype 2 and 3 it is 24 weeks. In slow responders an extension of further therapy over the following 24 weeks in all of the above groups is recommended.

• Checking IL28 B polymorphism before the start of therapy, to ensure better prediction of responsiveness to anti-viral therapy, is recommended.

• In patients with liver cirrhosis or failure to therapy, periodic monitoring is recommended.

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بـــــزودی از هـــــمین نـــویســـنده

شـرکت تعـاونـی پزشـکان سـلامت پژوهـان کـوثـر

Author message:

Thalassemia patients have high prevalence rates of hepatitis C virus (HCV) infections. Recent improvements in the survival of these patients are a result of more services in the control of iron overload, the provision of safe blood and better control of complications. Today, liver disease is the main cause of mortality in thalassemia patients throughout the world. Unfortunately, there are inadequate policies in most thalassemia centers for the control of HCV infections. I considered it imperative to provide a book from A to Z for health professionals regarding the epidemiology, screening, diagnosis and treatment of HCV infection in this high risk group. My hope is for better control of HCV in thalassemia patients in the world, especially in the Mediterranean region.

Author information:

Alavian is a professor of medicine and hepatologist, he established the first hepatitis clinic in 1995, at the Iranian Blood Transfusion Service in Tehran, and he is one of the founders of the Iranian Charity for Liver Support in Tehran, established in 1995. He has been the associate editor of the Journal of Clinical Virology from 2004. Prof.Alavian works as an advisor and consultant on national program projects for the control of hepatitis in Iran and he is also the founder and Editor-in-chief of Hepatitis monthly journal. He has been a member of the National Committee for Hepatitis in the Iranian Ministry of Health and Medical Education since 1995. Alavian is an experienced researcher and hepatologist who has been actively involved in various national multicenter clinical trials and basic scientific projects related to viral hepatitis over the past 19 years. He has authored/co-authored over 320 articles in both local and international journals. He was the principal investigator in numerous clinical trials related to the management and treatment of hepatitis C and B patients. His main interests are; health policy, epidemiological aspects of viral hepatitis, and methods of integrating new protocols for the control of these infections. He is also interested in clinical trials of emerging medications for hepatitis B virus and hepatitis C virus infections, along with the treatment of viral hepatitis in particular diseases, including thalassemia and hemophilia. He is the founder and director of the Middle East Liver Disease (MELD) Centers which were established in Iran, in 2012, and the program has expanded throughout the entire region with the collaboration of scientists in both Middle East and Middle Asian countries.

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