REVIEW ARTICLE

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Treatment of HCV Infection in Multitransfused Thalassemic Patients: Does Liver Iron Status Affect the Outcome of Response?

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Introduction

Patients with transfusion dependent thalassemia (TDT) require blood transfusion program throughout their life to sustain their growth and development during childhood. Transfusion not only exposes these patients to increased risk of blood borne viruses (the most important one is HCV infection)[(1)], but also causes an inevitable accumulation in body iron[(2)]. Regular chelating program can delay the secondary iron overload but not completely avert the development of hepatic fibrosis. The secondary Iron overload and HCV infection are the two main causes of chronic liver fibrosis in patients with TDT[(3)], which is a common cause of death after the age of 15 in TDT patients[(4)]. Notably in the last 3 decades we have witnessed profound changes in the management of patients with thalassemia major. Regular red blood cell transfusions and iron chelating permit a normal development throughout childhood, and extend survival. So treatment of HCV infection would have a great influence in the survival of a great number of TDT patients who pass their second decade of life.

Iran is located in thalassemia belt with more than 25,000 registered TDT. Epidemiologic studies have shown that around 20 to 40% of Iranian TDT patients are infected with HCV virus[(5,6,7)]. It should be mentioned that after initiation of donor screening for HCV in 1995 and exclusion of high risk groups from donation pool, the prevalence of HCV infection in thalassemic patients had decreased significantly[(7a)]. On the other hand, similar rate of HCV infection has been shown in TDT patients worldwide[(8)], which in turn puts another emphasis on the importance of HCV treatment in this group of patients.

History of HCV Treatment in Thalassemia

Interferon-alpha (IFN-a) monotherapy is currently approved as the first line treatment for HCV infection in TDT patients. Because of hemolytic complications of ribavirin, currently combination of IFN and ribavirin is preserved for IFN non-responders and only under investigational situations[(8)].

The concept that hepatic iron content might influence the response to interferon therapy was first described in 1994 by Van Thiel *et al.*[(9)] and by Olynyk *et al.* in 1995[(10)]. They retrospectively measured hepatic iron concentration (HIC) in HCV infected patients who had been treated with interferon and showed that the biochemical and virological response was better in subjects with less HIC and majority of the patients with HIC more than 1100 mg/g of dry weight of liver had not responded to interferon therapy. Based on the above studies during 1990s, it was not unwise to theorize that TDT patients who have a very high HIC due to secondary hemochromatosis would have a poor response to IFN monotherapy. However, there were two studies that evaluated the response of IFN monotherapy in thalassemic children, both of which were against the above theory; the first was the Clemente study in 1994[(11)], which reported a sustained virological response (SVR) after 6 months of IFN monotherapy in 19 out of 51 (37%)

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thalassemic children (with mean age of 14 years old) with chronic HCV infection and the second one was Di Marco study in 1997[12], which showed that 28 out of 70 (40%) of children (mean age 14.1 years old) with thalassemia achieved an SVR after 12 months of interferon monotherapy. Considering the Poynard *et al.* meta-analysis in 1996[13], which showed that the overall SVR with IFN monotherapy in non-thalassemic subjects was less than 30%, a preliminary conclusion could have struck our mind that the high HIC of HCV infected thalassemic children does not affect the response to IFN monotherapy. So other host or viral factors such as patient's age, short duration of infection (because according to Thalassemic International Federation [TIF] guideline, all thalassemic patients should undergo at least annual screening for HCV antibody)[5], degree of baseline liver fibrosis, virus genotype and viral load might have a stronger correlation with the treatment outcome.

There are two recent studies which used IFN monotherapy in adult HCV infected TDT patients and both showed that high HIC in TDT patients could not preclude achieving a good SVR even in adult TDT patients with massive iron overload. The first study by Sievert *et al.*[14] in 2002 showed that 8 out of 28 (28%) achieved a durable (mean 66 months) SVR (intent-to-treat approach) and the mean age of patients was 26 (range 15-45). In this study HIC was measured and there was no significant difference between responders and non-responders. The second study was performed in Iran by our group[15], where -by an intent-to-treat approach- we found a durable SVR of 24.1% (7 out of 29, mean post treatment follow up of 12 months) and mean age of 24 (range 13 to 56).

We believe that besides early HCV diagnosis, low age and consequently lower fibrosis score at diagnosis, which has shown to be correlated more reliably than iron with the treatment response[10], the recently shown antiviral effect of desferroxamine, mostly evident on HBV[17] and HIV[18] may intensify the antiviral effect of IFN on HCV.

Recent Advances in the Treatment of HCV

Attaching a large polyethylene glycol (PEG) molecule to the interferon-alpha protein (pegylated interferon [PEG-IFN]) was a major advance in the treatment of hepatitis C infection. It causes a sustained therapeutic concentration of interferon over the weekly dosing intervals and prolonged biological activity, which in turn has shown to increase (nearly double) the sustained response of conventional IFN in non-thalassemic subjects[19]. There is still a lack of clinical studies upon PEG-IFN monotherapy in thalassemic patients. It is now around 2 years that we have been using PEG-IFN monotherapy in thalassemic patients. In our first multicenter study[20], we prospectively included 32 HCV infected adult TDT patients and after 48 weeks of 180 µgr PEGASYS once a week, we had 60.8% SVR. Considering that the mean age of patients of this study was 24 and more than 75% of patients were genotype 1, it is a brilliant response. Preliminary analysis of a recent randomized study presented in the 9th International Congress of Thalassemia 2003 showed that PEG-IFN monotherapy was well tolerated and had a significantly better end of treatment response than conventional IFN monotherapy[21].

In our opinion, there are two aspects to consider:

1) Looking from patients' view: thalassemic patients are a suffering group, who not only are forced to bear many hours per day a desferroxamine pump over their skin in order to get rid of the extra iron out of their body, but also should receive pack cell transfusion every 15-25 days to attain their growth and development. For these special patients, we think weekly IFN makes a lot of difference over a 3 times per week.
2) Looking from scientific view: our two limited experiences indicate that the cure of HCV-related liver disease in TDT patients is not unattainable and may be reached with the safe and tolerable PEG-IFN preparation in a sizable portion of cases (more than 60% SVR compared to 24% of SVR with conventional IFN).

So we recommend initial therapy with PEG-IFN instead of conventional IFN in every TDT patient which is a candidate for HCV treatment.

We should also mention that efforts and trials are going on to increase the rate of SVR by using IFN and ribavirin[22,23,24], but all these studies are preliminary with a small number of patients. On the other hand, because ribavirin is contraindicated in hemoglobinopathies, those TDT patients who use it should be under close (weekly) observation during the study period and be in an investigational situation. Combination of IFN and amantadine (AMA), which has been shown to be superior to IFN monotherapy in non-thalassemic patients[25], could potentially be another option to be used in thalassemic patients. In a randomized controlled study we showed that although there was no significant deference between the end of treatment response of patients receiving IFN plus AMA versus

IFN alone, the SVR was significantly increased in IFN+AMA group[26].

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