EDITORIAL

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Are the Real HCV Infection Features in Iranian Patients the Same As What Is Expected?

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Hepatitis Monthly issue 7 contained four clinical trials of pegylated interferon (Peg-IFN) plus ribavirin for Iranian patients with chronic hepatitis C infection conducted in four various centers[1-4]. Apart from one trial[2], which enrolled only patients with inherited bleeding disorders, three others enrolled heterogeneous HCV infected populations. However, reported sustained virologic response (SVR) rate was varied from 50% to 78% in these studies. This wide SVR range might make difficulties for the readers to gain clear data regarding efficacy of this therapeutic regimen on Iranian patients.

Almost analogous inclusion and exclusion criteria as well as the details of these four studies allow us to intervene and join the cases and reanalyze the data from a single pool. However, the slight differences among these studies will obviously diminish the accuracy and make us discuss the results conservatively. For instance, in the study by Merat *et al.* none of the patients underwent liver biopsy[2] or Zali *et al.* excluded cirrhotic patients from the study[4]. Moreover, the sensitivities of RT-PCR tests applied to define response to treatment were varied from 100 copies/ml to 600 copies/ml in various studies. In spite of these inevitable biases, our intervention is able to provide useful information.

To analyze the data, we applied intention to treat analysis (ITT). ITT analysis is generally interpreted as including all patients who received at least one dose of medication(s), regardless of whether they actually satisfied the entry criteria, the treatment actually received, and subsequent withdrawal or deviation from the protocol[5]. Therefore, all patients who do not complete the study are considered to have failure to treatment. It is a strategy to avoid the problems created by omitting dropouts and noncompliant patients, which can introduce bias in the trial, and overestimate clinical effectiveness. Although there is a debate about the validity of excluding specific cases within each of these categories from an ITT analysis, clinical effectiveness may be overestimated if an ITT analysis is not done[5]. This is the point that was neglected in one study[5], in which despite of claiming to apply ITT analysis, the cases withdrawn after the initial doses were excluded from analysis.

A total number of 169 patients were enrolled in these four studies. One hundred and one patients achieved SVR. Thus, an SVR rate of 60.3% was found in the study population.

There are two well-known, comprehensive trials in this issue enrolling a large study population from multiple sites in Europe, North America, Australia and Asia by Manns *et al.*[6] and Fried *et al.*[7]. Both studies were on an ITT basis and the study methods were almost similar to those of Iranian studies. These two trials reported an SVR rate of at most 54% and 56%, respectively for Peg-IFN plus ribavirin therapy, which are around and even slightly lower than our SVR rate. If we compare the available baseline characteristics of sample populations of studies by Manns *et al.* and Fried *et al.* with those in Iranian studies, we will gain

Table 1: A number of characteristics of sample populations and SVR in the studies

		Manns *et al.*	Fried *et al.*	Iranians
Mean age (yrs)		43	42.8	38.3
Male (%)		68	72	86.3
Mode of transmission (%)*	Transfusion	22	19	50.0
	Intra-venous drug abuse	62	42	21.4
	Others/ Unknown	16	39	28.5
Cirrhosis (%)		100	100	6.4**
Naïve (%)		54	56	73.9
SVR (%)		54	56	60.3

* Three studies (1, 2, 3) provided data (n=112).

** Two studies (1, 4) provided data (n=109).

interesting findings (**Table 1**).

Study populations were roughly similar in regard to mean age. The male ratio in Iranian studies was fairly higher. In addition, drug abuse was more frequent in the population studied by Manns *et al.* and Fried *et al.*, while transfusion was the prominent risk factor in Iranian patients. On the other hand, fewer Iranian patients were cirrhotic although only two Iranian studies presented data in this regard[1,4]. More importantly, Manns *et al.* and Fried *et al.* enrolled only naïve patients while only 155 out of 169 cases (73.9%) of Iranian patients were naïve. It means that more than a quarter of Iranian patients had a history of unsuccessful interferon based therapy. Although some other baseline variables such as baseline HCV viral load were not provided in Iranian studies, higher rate of transfusion is a clue suggesting probable higher viral load in Iranian population. Considering the available pretreatment factors of the study populations in Manns *et al.* and Fried *et al* studies and Iranian studies, we found the Iranian patients more difficult to treat. However, we found that SVR in Iranian patients was equal to or even slightly higher than SVRs reported by them. Interestingly, considering a couple of elegant points in Iranian studies including: 7 patients received Peg-IFN monotherapy due to thalassemia major, 5 patients received only a 24-week course of treatment, 6 patients missed the follow up period in spite of clearing HCV RNA at week 48 and necessarily considered nonresponders in analysis, we can suggest that SVR in Iranian patients might be even higher than what was found. Furthermore, if we analyzed the naïve patients separately (123 cases), SVR rate would rise even up to as high as 64.2-66.6%. Therefore, the question is: Why was the SVR rate in Iranian patients higher than what was expected?

The only issue left overlooked is HCV genotype distribution. Manns *et al.* and Fried *et al.* reported 68% and 65% of HCV genotype 1 -difficult to treat- in their study populations. In Iranian studies, the data are insufficient in this regard. Merat *et al.* detected genotype 1 in 60% of 20 patients evaluated[2]. In two most recently reported studies investigating HCV genotype in Iranian patients, the genotype 1 rates of 55% and 63% were reported[8,9]. Thus, the rate of difficult to treat genotype appears not to have considerable difference in Iranian population compared with population studied by Manns *et al.* and Fried *et al.* If it is the case, can we claim that our genotype 1 patients will respond to treatment better than the similar genotype in other populations? Are Iranian patients with genotype 1 not as difficult to treat as what expected?

As a hypothesis, the Iranian patients infected with HCV genotype 1 probably are not analogous to the patients who apparently have the similar genotype in other studies. An evidence to support this suggestion is the genotype 1 spectrum in Iranian patients. Despite similar HCV genotype 1 distribution in Iranian patients with the patients studied by Manns *et al.* and Fried *et al.*, the rate of HCV genotype 1 subtypes is strikingly different among populations. While 1a/1b ratio was 31/34 in the study by Fried *et al.*[7] (Manns *et al.* did not report such data), it was reported 45/15 by Merat *et al.*[2], 47/4 by Samimi-Rad *et al.*[8] and 51/12 by Ahmadipour *et al.*[9]. Then, the majority of Iranian patients were infected with genotype 1a subtype. The suggestion is that genotype 1a, which is more prevalent in Iranian patients, probably is not as difficult to treat as genotype 1b. If it is the case, we will observe higher response to treatment in Iranian patients with genotype 1 than other studies.

As the second suggestion, each of HCV genotypes 1a, 1b etc. may have its own subtypes which differ from each other regarding IFN resistance and difficulty to treat. Then the Iranian patients with HCV genotype 1 may be infected with subtypes different from the patients who apparently have similar genotype in other studies. It is obvious that these suggestions need to be investigated in future researches.

Safety is a major concern of new therapeutic agents that could be different in various races and ethnicities. In the study by Fried *et al.*[7], in which the patients received Pegasys®, the therapy was

discontinued in around 10% of patients due to clinical adverse events or laboratory abnormalities and dose modification of Pegasys® and/or ribavirin was required in 36-45%. However, only in 4 patients of Iranian studies (around 6%) therapy was discontinued and 45 patients (around 27%) needed dose modification. These results could suggest an overall better tolerability of this regimen in Iranian patients.

On the basis of the study on safety assessment of Pegasys® plus ribavirin therapy, neutropenia was reported in 21% of patients, anemia in 11% and thrombocytopenia in less than 10% of patients[10]. Totally, anemia and thrombocytopenia were found in 10% and 6 % of Iranian patients, respectively, which is near to the last report. However, only 10% of Iranian patients experienced neutropenia, which is much lower than what was reported in last study.

In summary, Iranian patients tolerated the medications well. Moreover, the probability of side effect occurrence is lower than what was expected in some cases. We hope we can achieve the same result with the Iranian pegylated Interferon in our future studies.

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