Outcome of hepatitis C patients in a community with predominant genotype 3 with standard-of-care treatment before and after advent of direct-acting antivirals: A retrospective-cum-prospective study

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Abstract:
BACKGROUND AND OBJECTIVE: Chronic hepatitis, cirrhosis, and hepatocellular carcinoma are mainly caused by hepatitis C infection. It is a worldwide predominant pathogen and is one of the main causes of healthcare problem in Asia. In the last few decades, there has been a considerable change in the treatment regimen for hepatitis C virus. The objective of this research was to relate the treatment response with sustained viral response in various therapies which have been the standard of care from time to time.

MATERIALS AND METHODS: This hospital-based, retrospective-cum-prospective research span over a period of 2 years; we enrolled hepatitis C patients who attended the Department of Gastroenterology and Hepatology, Government Medical College, Srinagar, since June 2015 till May 2017. Subsequently, the database was prepared, containing all the relevant information about these patients.

RESULTS:

| Group            | Regimen                                      | Duration (weeks) | SVR (%) |
|------------------|----------------------------------------------|------------------|---------|
| Retrospective    | PegIFNα2a+ribavirin                           | 24               | 90.96   |
| group (n=200)    |                                              |                  |         |
| Prospective      | Sofosbuvir+ribavirin                          | 12               | 94.57   |
| group (n=290)    | Sofosbuvir+daclatasvir                        | 12               | 98.00   |
| Prospective      | Sofosbuvir+ribavirin + daclatasvir (in cirrhotics) | 24               | 83.33   |

SVR=Sustained viral response, PegIFNα2a=Pegylated interferon α2a

CONCLUSIONS: (i) In retrospective group: The overall efficacy (sustained viral response at 24 weeks [SVR-24]) of pegylated interferon α2a and ribavirin regimen was 90.96%. (ii) In prospective group: The efficacy (SVR) of different regimens was found to be as: sofosbuvir + ribavirin + daclatasvir (SVR-24, 83.33%); sofosbuvir + ribavirin (SVR-12, 94.57%); and sofosbuvir + daclatasvir (SVR-12, 98.00%).

Keywords: Direct-acting antivirals, early viral response, end of treatment response, hepatitis C, India, Kashmir, pegylated interferon, rapid viral response, sustained viral response

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How to cite this article: Kadla SA, Dar MA, Shah NA, Khan BA, Shah AI, Pathania R, et al. Outcome of hepatitis C patients in a community with predominant genotype 3 with standard-of-care treatment before and after advent of direct-acting antivirals: A retrospective-cum-prospective study. Indian J Pharmacol 2020;52:372-7.
**Introduction**

Hepatitis C virus (HCV), previously known as non-A, non-B viral hepatitis, was identified in 1989. Subsequently, its full genome was isolated by Choo et al.[1] Currently, HCV is one of the primary reasons known to cause chronic liver disease; 60%–70% of them belong to the Asian-Pacific Region.[2] Chronic hepatitis C infection is seen between 2.7 and 4.1 million people in the USA, and 15%–20% of carriers have developed liver cirrhosis within 20 years.

HCV affects individuals from all walks of life; the highest incidence ranges from 20 to 49 years. The prevalence ranges from as low as 0.4% in Western Europe to as high as 22% in Egypt and other parts of Africa.[3]

HCV infection is predominantly transmitted through parenteral exposure.[4] 2%–24% of patients subsequently progress toward cirrhosis following 20 years of occurrence of HCV infection with many established or potential aspects linked with the development of hepatic fibrosis.[5-7]

Management of chronic hepatitis C remains a big challenge in the field of hepatology over the last two and half decades. Hoofnagle and Schafer were the first to report pegylated interferon (PegIFN)α as a proficient therapy for hepatitis C; however, the relapse was quite frequent.[8] This was followed by treatment modifications, modification of dose, and duration in following years. The overall sustained viral response (SVR), which is considered an equivalent to cure, was better in higher doses and longer duration. However, because the higher doses caused more adverse effects, the standard of care was 3 million units of IFN three times a week for 12 months till 1998.[9] Therefore, the introduction of PegIFN was an important milestone in HCV therapy. After establishing PegIFN plus ribavirin as the standard of care in 2001, this treatment was optimized and individualized over a period of time till 2011.

The race for all oral antiviral treatment started with nonstructural (NS)-3/4A inhibitors, telaprevir and boceprevir; however, because of many reasons, these drugs did not gain importance though their addition decreased the duration of treatment and slightly increased rates of SVR. In early 2014, three very effective oral antivirals, viz., sofosbuvir, an NS-5B inhibitor with pan-genotypic effect and two NS-5A inhibitors, ledipasvir and daclatasvir, were approved simultaneously, and with their launch, the revolution of antiviral treatment started and a paradigm shift was declared when FDA permitted the use of sofosbuvir + daclatasvir (SD) over 12 weeks to treat HCV infections (genotype 3). The recommendation is founded on ALLY-3, a phase III study of the once-daily an NS-5A inhibitor (Daclatasvir) and NS-5B inhibitor (Sofosbuvir), SD, for 12 weeks for the treatment-naive noncirrhotics and for 24 weeks in the treatment exposed or cirrhotics.[10] Although the genotype 3 has been considered difficult to treat all over the world, we have a different observation altogether. Our genotype 3 patients did well even with interferon (IFN)–ribavirin combination and are doing excellent with the present regimens available with us. This prompted us to analyze the data which are compiled in the department of gastroenterology and hepatology retrospectively and to observe all-oral regimens prospectively.

**Aims and objectives**

1. To analyze the efficiency in different treatment protocols for hepatitis C patient groups using IFN-based regimens and those on direct-acting antivirals (DAAs)
2. To study the period of response in different regimens in HCV treatment
3. To study the outcome of treatment regimens with respect to drug intolerance, treatment failures, side effects, and cost-effectiveness
4. To recommend an ideal regimen for HCV.

**Materials and Methods**

This prospective-cum-retrospective research has been carried out in a tertiary care hospital, Department of Gastroenterology-Hepatology and Department of Medicine, Jammu and Kashmir (India). After ethical committee clearance (vide endorsement no. 177/ETH/GMC/ICM), for retrospective analysis, the data of 200 HCV patients (genotype 3) put on IFN + ribavirin combination from 2011 to 2014 were retrieved, tabulated, and analyzed as per demography and quantitative HCV RNA before, during, and after treatment for rapid viral response (RVR), end of treatment response (EOT), and SVR, respectively. The prospective group with 290 HCV patients (genotype 3) was studied for 2 years (July 2015 to June 2017). Outpatient department and inpatient department patients were enrolled for the purpose. While performing preoperative evaluation, evaluation of liver function tests (LFTs), blood donation, or in-field screening community camps, these patients were diagnosed with hepatitis C.

After a written consent, patients in the prospective group were properly evaluated. A thorough clinical examination was performed, and all baseline investigations were done which included a complete hemogram, kidney function tests, LFTs, coagulogram using ACL ELITE, ultrasonography focusing on features of chronic liver disease and portal hypertension, EGD for varices and PHG, HCV RNA viral load, and genotyping with HCV real-time PCR genotyping test. After complete
evaluation, patients were subjected to treatment. During 2015, the patients were initially administered sofosbuvir 400 mg + ribavirin (SR), as per the EASL and APASL guidelines 2015 (SR [weight based] was given to noncirrhotic patients for 12 weeks while as in cirrhotic patients for 24 weeks). During this period, the only DAA drug approved by the FDA was sofosbuvir. This drug was marketed in India around March–April 2015. A total of 166 patients (out of 290) were given this regimen (all were noncirrhotic). Then, the next DAA for genotype 3 was daclatasvir which was marketed in India in October 2016. Out of 290 patients, 100 patients were given sofosbuvir 400 mg + daclatasvir 60 mg (all were noncirrhotic). They were given this regimen as per the existing guidelines at that time. The remaining 24 patients out of 290 were cirrhotics and were administered sofosbuvir + daclatasvir + ribavirin (weight based) [SDR regimen] as per the existing guidelines. The overall treatment regimens and their percentage are given in Figure 1.

These patients were monitored with respect to worsening of disease and appearance of new symptoms and side effects. Further, the complete blood count and the periodic LFTs were also performed.

HCV quantitative RNA analysis was performed at week 4 (RVR), week 12 (EOT in noncirrhotics), and week 24 (EOT in cirrhotics and sustained viral response at 12 weeks [SVR-12] in noncirrhotics) and at 6 months post-EOT (SVR-24) in cirrhotics.

Those excluded from the study were genotypes other than genotype 3, patients with HCV and HIV coinfection, pregnant women, patients with a history of organ transplant, and chronic renal failure patients on hemodialysis.

**Statistical analysis**

Data were entered in Microsoft Excel spreadsheet. Frequency and percentage have been used to represent the definitive data. To analyze the relationship between the patient data and HCV RNA status, Chi-square test was employed. P < 0.05 is interpreted as statistically substantial. The records were explored by employing SPSS version 22.0 statistical software acquired by International Business Machines (IBM) company, developed by Norman H. Nie, Address: Corporate headquarters, 1 New Orchard Road Armonk, New York, USA 10504-1722.

**Results**

In the prospective group, the mean patient’s age came out to be 39.1 (±13.5) years (53.79% males and 46.20% females). The 20–29 years of age group was predominant, among which 30.77% were males and 31.34% were females.

In the retrospective group, the mean age was 38.6 (±9.03) years with 58% of them being males and 42% of them being females. The 30–39 years of age group was predominant among which 40.5% were males and 57.1% were females.

The age, gender distribution, and clinical characteristics (whatever was available in the retrospective group) were comparable in both groups, except those patients who had cirrhosis, as no cirrhotic patient was treated with IFN, and from the prospective group, only 24 cirrhotic patients received DAA.

As SVR-24 was considered the standard of response for the retrospective group, it was calculated for retrospective group. For this group (n = 200), 12 patients stopped the treatment in view of intolerable side effects or financial reasons, and as a result, only 188 patients were considered for final assessment. SVR-24 on PegIFNα2a + ribavirin (weight-based) regimen over 24 weeks was obtained in 90.96% of patients [Figure 2]. Seventeen out of 188 patients had relapse in this
combination [Figure 3] after the EOT. The adverse drug reactions in patients were also reported which included fatigue (45%), flu-like symptoms (40%), anemia (35%), thrombocytopenia (27%), depression (30%), neutropenia (12%), loss of appetite (25%), insomnia (32%), and anxiety (10%).

For prospective group \( (n = 290) \), SVR-12 was considered as standard of response, which is tabulated in Table 1.

The adverse drug reactions in patients were also reported which included fatigue (30%), headache (15%), and anemia (15%). None of the patients halted treatment owing to adverse drug events (ADEs) or financial constraints. It is very difficult to compare the two groups, as in the retrospective group, a response-guided treatment was given, and in the prospective group, only EOT and SVR are useful. Keeping in view the importance of SVR in both groups, it was given a special emphasis.

HCV RNA viral load was conducted at 12 weeks after completion of the treatment; SVR-12 was achieved in 83.33% of patients on SDR regimen in cirrhotic patients, 94.57% of patients on SR regimen in noncirrhotics, and 98% of patients on SD in noncirrhotics.

HCV RNA viral load was conducted at 24 weeks after completing the treatment; 90.96% of patients on PegIFN \( \alpha \) + ribavirin (weight-based) regimen exhibited SVR-24.

Discussion

Hepatitis C was treated with IFN for about two decades and IFN plus ribavirin were used for many years even when some serious side effects were encountered during the therapy. It was a dream come true for a hepatologist to have a more robust treatment for hepatitis C rather than IFN and ribavirin which became a reality in 2011 when DAAs came into practice and the research is still continuing.

For nearly 20 years, HCV treatment was based on boosting and modulating the innate immune response, and as a result, IFNs were thought to be the treatment of choice. Even before molecular cloning of HCV in 1989, a pilot study demonstrated the usefulness of IFN in non-A and non-B hepatitis patients, who were later on actually found to have HCV [12]. IFN-alpha monotherapy was approved by the FDA in 1991 based on two clinical trials which lasted for 6 months and showed a significant biochemical response [13,14].

Ribavirin, not effective as a single agent, did improve the outcome when combined with IFN; however, the exact mechanism of action is still elusive. The combination of ribavirin and conventional PegIFN was thought of as a major breakthrough which tripled the SVR. The conclusion of the twentieth century brought about the

Table 1: SVR-12 as standard of response in Prospective Group \((n=290)\)

| Group | Regimen                      | Duration (weeks) | SVR (%) |
|-------|------------------------------|------------------|---------|
| Prospective group \((n=290)\) | Sofosbuvir + ribavirin     | 12               | 94.57   |
|       | Sofosbuvir + daclatasvir    | 12               | 98.00   |
|       | Sofosbuvir + ribavirin + daclatasvir | 24               | 83.33   |

Table 2: Response guided outcome in the Prospective Group \((n=290)\)

| Group       | RVR (%) | EVR (%) | EOT (%) | SVR (%) |
|-------------|---------|---------|---------|---------|
| Cirrhotics  | 75%     | 87.50%  | 100%    | 83.33%  |
| Non Cirrhotics | 95.86% | 95.86%  | 95.86%  |         |

*With reference to patient history, clinical examination and USG findings.

RVR = Rapid viral response, EVR = Early viral response, EOT = End of treatment, SVR = Sustained viral response, USG = Ultrasonography

Table 3: Comparison of results in various published studies

| Study       | Regimen                                      | SVR                  |
|-------------|----------------------------------------------|----------------------|
| Valence[24] | Sofosbuvir (400 mg) + ribavirin (weight based) (given for 24 weeks) | 93% in treatment naive 97% in cirrhotic |
| Fission[25] | Sofosbuvir (400 mg) + ribavirin (weight based) (given for 12 weeks) | 63% |
| Positron[26] | Sofosbuvir (400 mg) + ribavirin (weight based) (given for 12 weeks) | 61% |
| Fusion[27] | Sofosbuvir (400 mg) + ribavirin (weight based) (given for 16 weeks) | 30% for 12 weeks 62% for 16 weeks |
| Phase III ALLY[28] | Sofosbuvir (400 mg) + daclatasvir (60 mg) (given for 12 weeks) | 90% overall 97% in treatment naive 58% in cirrhotic |

SVR = Sustained viral response
PegIFN products which led to an increase in SVR to nearly 40%–50%.

Nearly a decade later, boceprevir and telaprevir, the first DAAs, were approved in 2011 and with their introduction started the revolution of hepatitis C treatment. Two years later, with the introduction of simeprevir and sofosbuvir (2013) and then a fixed-dose combination of ledipasvir and sofosbuvir (2014), ombitasvir/paritaprevir/ritonavir plus dasabuvir (2014), and daclatasvir (2015), the SVR rates exceeded 90%. As a result, the treatment guidelines went on changing so rapidly that a website was created to choose the best treatment for a particular patient.[15]

Since the combination of IFN + ribavirin has given rise to many ADEs, many patients were either ineligible to this combination or would stop it halfway. ADEs were reported with varying severity in up to 94% of patients receiving this combination. These included anemia, thrombocytopenia, influenza-like symptoms, and depression. The dropout rate was as high as 3%–17% with poor SVR rates.[16]

In May 2011, with the authorization of first generation DAA i.e. Boceprevir - a NS-3 serine protease inhibitor, a paradigm change and an innovative era started in the treatment of Hepatitis C. Unfortunately, this drug is known to cause hematological ADEs and its addition to ribavirin–IFN combination worsened the anemia, neutropenia, and thrombocytopenia in addition to dysgeusia.[17]

Telaprevir, an NS-3/4a protease inhibitor, was the second FDA-approved drug in May 2011. This was also added to IFN + ribavirin combination and this also worsened the ADE, especially anemia in addition to its hallmark side effects such as rash, pruritus, and anorectal burning.[17]

In November 2013, FDA approved the first second-generation DAA - Simeprevir, that was utilized in combination with Interferon and Ribavirin. This drug also had multiple ADEs such as rash, pruritus, and gastrointestinal disturbances.[18]

Sofosbuvir was the first NS-5B polymerase inhibitors introduced in December 2013. Combinations such as SR; sofosbuvir + ledipasvir; SD; and sofosbuvir + simeprevir became highlights of all guidelines and favorites of all hepatologists.[19-25]

These combinations were overall well tolerated except for few, mild ADEs, and the combinations were genotype specific. However, with the introduction of velpatasvir, a pan-genotypic DAA, the treatment has become almost ideal now.

Ours is a community with predominant genotype 3, and we had a general observation that our patients do well even with PegIFN; however, we never documented it. Since the introduction of sofosbuvir in 2013, we, like our other colleagues throughout India, switched over to this combination. For a long time, we did not use a ribavirin-free regimen as ledipasvir and daclatasvir were not available in the market. Moreover, SR combination was given free by the Department of Health and Family Welfare in many villages of South Kashmir. We enrolled all patients prospectively since the introduction of SR and went on enrolling patients who were later on put on SD as well. We collected the IFN data retrospectively with some lacunae and deficiencies.

In the retrospective group, we had treated noncirrhotic patients fearing decompensation and liver failure in the absence of transplant facilities at our center.[13-16] PegIFNo2a at a standard dosage, i.e., 180 mcg, with dose modifications as and when required, plus weight-based oral ribavirin, was given to patients. 96.50% achieved RVR, 99% achieved an early viral response (EVR), but 6% of patients discontinued the treatment either because of financial constraints, intolerance, or severe ADEs as early as 4 weeks and as late as 12 weeks, and final analysis was done on 188 patients only. All the 188 patients accomplished the treatment (EOT). The results of our study were superior to the results published by Fabris et al., who achieved the SVR of 82% and 89.7%, respectively, for 16 and 24-week regimens,[17] and also to the results from the study published by Tohra et al., who had achieved 84% RVR, 81% EVR, and only 65% SVR in their study of 99 patients.[19] Similarly, our results were better than many other studies such as Mecenate et al.,[20] Waheed, [21] and Brochet et al.[22] As far as tolerance to IFNs is concerned, it has been better in our study than some other studies.[22] With these observations, it looks like that we are dealing with a different genotype 3 which is definitely more sensitive to IFN-based treatment, and our patients did tolerate the treatment relatively well. However, tolerance to IFNs and cost remains a major factor against the use of these drugs when we compare it with newer regimens available with us.

The response guided results of the prospective group are summarized in Table 2.

Results of our study are comparable with the results of Phase III ALLY-3 study.[10] In noncirrhotic group, SR group achieved an SVR of 94.57% and SD group achieved an SVR of 98% with excellent tolerance and minimal or no ADEs. With presently available hepatitis C drugs, genotype 3 is considered challenging to treat. In this context, the results of various published studies are compared in Table 3.

Conclusions

The treatment of hepatitis C has evolved over the years
and is almost near perfection. Genotype 3 seems to be sensitive to presently available treatment in our setup which otherwise was considered difficult genotype to treat. Our genotype 3 patients responded well to IFNs and even better to all oral antivirals. As dropout rates, side effects, and cost factors favor the oral antivirals, the IFN-based regimens need not to be used in present scenario. The ribavirin should be used only in cirrhotics or in treatment-exposed patients. Sofosbuvir and daclatasvir combination is the best one for genotype 3 in North India though this study did not include the patients on velpatasvir a pan-genotype DAA.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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