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A systematic review of treatment response rates in Pakistani hepatitis C virus patients; current prospects and future challenges

Muhammad Ali, PhD[a,*], Samia Afzal, PhD[b], Asad Zia, MPhil[a], Ahmed Hassan, MPhil[a], Ali Talha Khalil, PhD[a], Muhammad Ovais, MPhil[a], Zabta Khan Shinwari, PhD[a], Muhammad Idrees, PhD[b,c,d]

Abstract

Background: The estimated hepatitis C virus (HCV) carriers are approximately 10 million in Pakistan which usually progresses to chronic hepatitis, with rare cases of spontaneous viral eradication. The present article reviews the treatment status of HCV infection in Pakistani population and various factors associated with the treatment response rates.

Methods: Literature on anti-HCV therapy was searched in PubMed, Google Scholar and PakMediNet. Thirty three different studies representing different geographic regions of Pakistan published from 2002 to 2016 were included in the present review. Weighted mean, standard error estimates (SE) and standard deviation (SD) were determined for each population group.

Results: Mean value for sustained virological response (SVR) for standard IFN plus ribavirin (RBV) combination therapy was 68.38% ±14.13% (range 33.8%–87.10%; SE 3.08) and pegylated-IFN plus RBV combination therapy 64.38% ±8.68% (range 55.0%–76.00%; SE 3.88). The lowest value for SVR has been reported to be 24.3% (for genotype 1; administering INF-α 2b 3MU 3 times/week and RBV 1000–1200 mg/day for 48 weeks) while highest of 87.5% (genotype 3a; INF-α 2a 3MU 3 times/week and RBV 1000–1200 mg/day for 24 weeks). The mean value for rapid virological response (RVR) was found to be 48.18% ±29.20% (SE 9.73). As PEG-interferon and direct acting antivirals (DAAs) are relatively expensive, interferon-alfa (IFN-α) and RBV combination therapy have been used widely to treat HCV infected patients in Pakistan for the last one and half decade. On average, 2.45% of the patients discontinued treatment due to severe side effects.

Conclusion: We encourage further studies on understanding host and viral factors associated with specific focus on harder to treat viral variants (relapsers and nonresponders). These variants are currently rising in the country.

Abbreviations: DAA = direct-acting antiviral, ETR = end of treatment response, HBV = hepatitis B virus, HCC = hepatocellular carcinoma, HCV = hepatitis C virus, HLA = human leukocyte antigen, IFN = interferon, IL = interleukin, RBV = ribavirin, SE = standard error estimates, SVR = sustained virological response.

Keywords: direct acting antivirals, interferon, nonresponders, ribavirin, sustained virological response

1. Introduction

Chronic infection with hepatitis C virus (HCV) symbolize an important healthcare problem and is estimated to cause infection in up to 170 to 200 million people throughout the world[1,2] with approximately 10 million in Pakistan.[3] INF are cytokines (glycoproteins) released by the cells during infections. Naturally, the presence of double-stranded viral RNA in infected cells activates type-I interferon (IFN)-α and β genes at transcription level.[4,5] Almost all of these usually progresses to chronic hepatitis, with rare cases of spontaneous viral eradication.[3,6] IFN-α therapy was approved for the treatment of HCV infection in 1991 which showed very low virological response rates of <20% sustained virological response (SVR). In 1998, a higher response rates were reported by the administration of ribavirin (RBV) in combination with INF. In 2001, the response rate to the antiviral therapy was further improved by the introduction of pegylated-IFN; a more stabilized drug.[7]

In Pakistan since the last about 2 decades, combination treatment with IFN-α and RBV continues to be used widely in routine practice in HCV infected patients.[8,9] Frequency of HCV infection in Pakistani population is significantly higher as compared to the neighboring countries like Iran, India, Afghanistan, Myanmar and Nepal.[10] Moreover, full length HCV (genotype 3a) isolate from Pakistan has been described to

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[a] Department of Biotechnology, Quaid-i-Azam University Islamabad, Islamabad, [b] Division of Molecular Virology, National Center of Excellence in Molecular Biology (CEMB), [c] Center for Applied Molecular Biology (CAMB), University of the Punjab, Lahore, [d] Hazara University Mansehra, Mansehra, Pakistan.

[*] Correspondence: Muhammad Ali, Department of Biotechnology, Quaid-i-Azam University Islamabad, Islamabad 45320, Pakistan (e-mail: muhammad.ali@qau.edu.pk, ali_biotech01@yahoo.com).

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be genetically different from those (HCV-3a isolates) from the rest of the world.[11] In addition, more recently emerging HCV variants has been reported in Pakistani patients in response to IFN plus RBV antiviral therapy.[12] Nevertheless, studies on estimating treatment response rates to the antiviral therapy in Pakistani population are still not clear, as limited numbers of reports are available on this subject[8,13] mostly targeting small population groups. Therefore, the present review was designed to assess the treatment response rates; factors influencing treatment response rates and side effects associated with the antiviral therapies in HCV infected Pakistani patients.

2. Methods

2.1. Literature search

2.1.1. Antiviral therapy response. For estimating the antiviral response rates in Pakistani HCV infected patients; articles were searched in PubMed, PakMediNet and Google Scholar by using keywords like; Treatment of HCV in Pakistan, HCV treatment response rates in Pakistan, HCV therapy in Pakistan, factors influencing treatment response rates, HCV infection in Pakistani population, emergence of resistance in HCV, HCV treatment, and ethnicity and supportive therapy for HCV patients (Fig. 1). A total of 33 studies published from 2002 to 2016 fulfilled the inclusion criteria and were included in the present review.

2.1.2. Inclusion criteria. Inclusion criteria were designed to screen the irrelevant references or articles with the information not sufficient to be included in the present study. Studies full filling the following criteria were included:

(1) Samples were collected from Pakistani individuals.
(2) An obvious description of the methods of detection of HCV infection and treatment.
(3) Information about the number of individuals studied and their residing area were reported.
(4) Duration of the treatment was reported.
(5) End of treatment response (ETR) was reported for the treated patients.
(6) The following simple formulas were used to describe the data from different manuscript in a similar way:

Total Patients = No. of patients with ETR + No. of non-responders

Total Patients = No. of patients with SVR + No. of relapsed patients + No. of nonresponders

(7) All the articles with the incomplete information were excluded.

Studies describing side effects of anti-HCV therapy, factors influencing treatment response, treatment status in resistant HCV patients, and supportive therapies administered in Pakistani HCV infected patients were included to discuss the subject in detail.

2.2. Full text review of the selected articles

Two of the authors independently reviewed all the full-text articles obtained during the electronic search. Data from the eligible articles were extracted on the electronic spread-sheet. All the disagreements were discussed and were referred to a third reviewer for final decision. The data extracted from the selected studies include location of the population, number of individuals reported in the study, HCV genotype, type and duration of therapy, percentage of patients with SVR, % relapsers and percentage of nonresponders to therapy. The study was conducted using PRISMA statement as described previously by Moher et al.[14] As the current manuscript is a review article, it does not require ethical approval from the institutional ethical

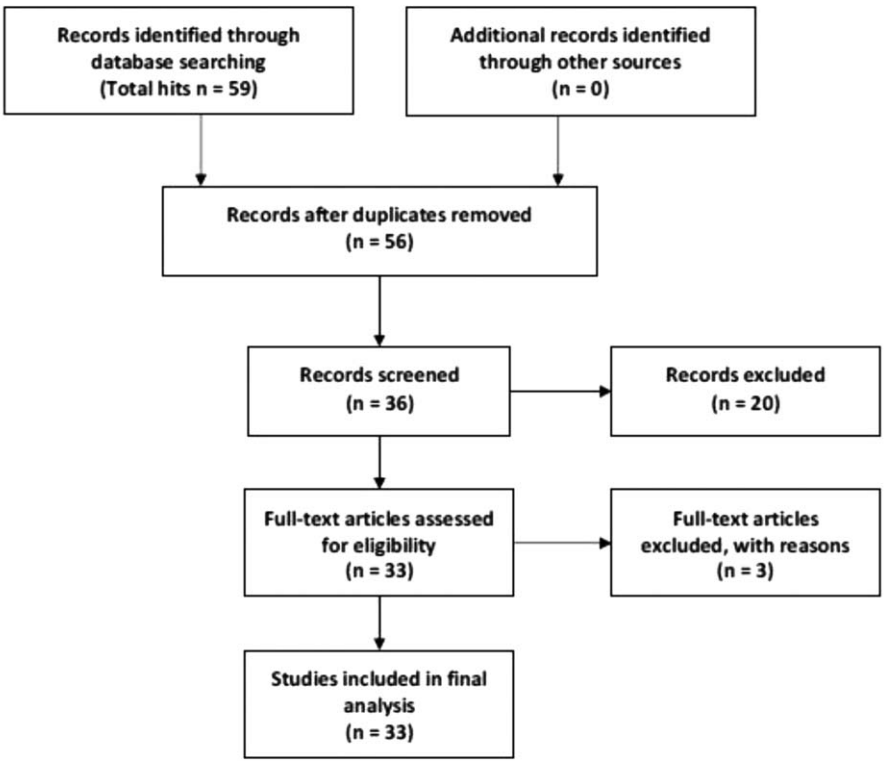

Figure 1. Study design.

committee. All the data have been obtained from the previously published articles and the concerned manuscripts are properly cited.

2.3. Statistical analysis

The data was analyzed by using SPSS software package (version 16.0). Statistical parameters like mean, standard deviation and standard error estimates (SE) were determined for the data reporting percent ETR, SVR, relapsers, and nonresponders to antiviral therapies. Paired sample *t* test was used to assess the association between the variables.

3. Results and discussion

3.1. Treatment response rates in Pakistani population

Figure 2 shows details about the total number of patients and % SVR rates in each individual study (further details of each study are included in Tables 1–3). We further calculated the mean percent values for ETR, SVR, relapsers and nonresponders. Twenty two different studies showed mean percent value for ETR (%ETR) of 76.21% ± 13.8% (SE 2.52).[3,6,8,9,15–33] Mean value for SVR was 60.70% ± 17.55% (SE 3.51),[3,6,8,9,16–30,32,33] while 25 different studies reported that 21.31% ± 11.33% (SE 2.26%) of the patients were found nonresponders to the antiviral therapy.[3,6,8,9,15–35] The mean value for rapid virological response were found 48.18% ± 29.20 (SE 9.73)[6,17,18,24,25,27–29,36] and treatment relapsers 14.21% ± 8.32% (SE 1.66).[3,6,8,9,15–36] The minimum value for SVR has been reported to be 24.3% (for genotype 1) using INF-α 2b plus RBV combination therapy for 48 weeks[3] which is in agreement with previously described reports describing.[37]

3.2. Treatment response rates in different genotypes

Ten studies report treatment response in patients infected with HCV-3a. The mean SVR value for this specific genotype is 65.093% ± 14.94% (SE 4.31).[3,6,8,15–18,24,28,33] In nine studies genotype was not determined; mean SVR rates in these studies were 69.06% ± 17.15% (SE 5.17)[20,23,26,27,29,30,32,38] (see Tables 1 and 2 for details). In 2 studies both genotype 1a and 3a patients were treated with IFN plus RBV therapy and SVR rates of 73.695% ± 1.41% (SE 0.995) is reported.[19,28] Only 2 studies included all the different genotypes and reported average SVR rates of 57.51% ± 7.75 (SE 5.48).[3,22] These results show that HCV response rates in Pakistani HCV patients is quite diverse depending on viral genotype.

The most prevalent HCV genotype in Pakistan is HCV-3a (>70%) followed by 3b (estimated 9%) and 1a (about 3%).[39] A study involving genotype analysis in the decade 2000 to 2010 reported change in the prevalence pattern of different genotypes prevalent in the country.[40] It is an established fact that the effectiveness of the INF and RBV combination therapy depends on the HCV genotype; toxicity associated with the treatment and parameters that effect treatment response. Paired sample *t* test revealed significant association ($P < 0.005$) between HCV-genotype and %SVR rates. In addition, significant association between therapy type and genotype ($P = 0.011$).

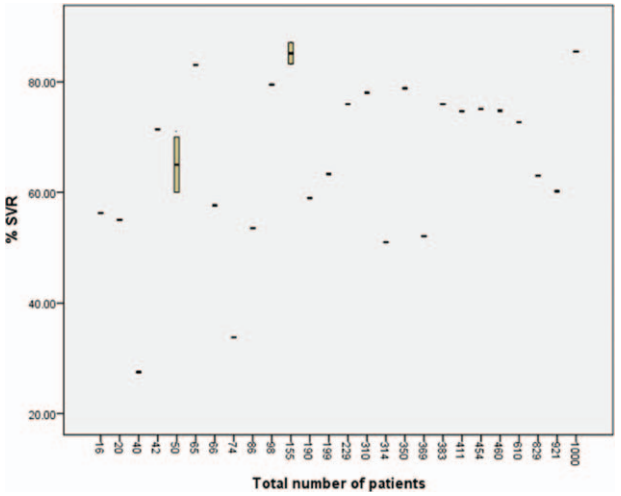

Figure 2. Illustration of total number of patients and % sustained virological response in each representative studies. The minimum numbers of patients (16) were studied by Khalid et al[32] and maximum of 1000 patients have been studied by Ali and Irum.[30] The corresponding %SVR rates have been plotted on y-axis. SVR = sustained virological response.

3.3. Treatment of HCV infected Pakistani population with other complications

In a study Pakistani patients with HCV associated hepatocellular carcinoma (HCC) were found with the lowest SVR rates of 0%.[41] Another study from Pakistan[42] reported that combination therapy (Pegylated INF-α 2a plus RBV for 48 weeks) failed to treat HCV/hepatitis B virus (HBV) coinfected patients as either both HCV and HBV or only HBV infection remained detected at the end of treatment. Abbas et al[43] reported a very low SVR rates of 13.33% (INFα 3 MU 3 times per week plus RBV 200–1000 mg per day for 6–12 months) in patients with HCV related glomerulopathy and recommended that such patients should be treated with modified doses for longer durations to achieve high treatment response. However, data regarding HCV treatment response rates in the patients with other complication including coinfected with viruses like HBV, HDV and HIV is still limited.

3.4. Treatment of resistant HCV infection in Pakistani population

Patients nonresponders or relapsed to IFN based therapies has been reported difficult to treat as compared to treatment naive HCV infected individuals. Butt et al[24] reported treatment response rates of 40% (6/15) in patients previously non-responding to antiviral therapy and 52.6% (10/19) in relapsed Pakistani patients by the administration of peg-INF + RBV therapy. In another study, Khokhar et al[38] found a 49 year old patient nonresponder to INF plus RBV combination therapy (for 48 weeks and additional 24 weeks) followed by RBV and peg-INF (of 80 mcg/week) therapy. High dose of peg-INF (120 mcg/week) combined with RBV therapy for 48 weeks which resulted in SVR in that patient. These results show that nonresponders and relapsed patients can be treated with a high peg-INF dose in combination with RBV however; such patients must be closely observed for adverse effects of the therapy.

3.5. Side effects of the therapies

Thirteen different studies[3,9,15,17–19,25,27,30,32,34] reported an average of 2.45% Pakistani HCV-infected patients discontinued

Table 1

Treatment response rates in Pakistani HCV population.

Author	Region	Patients (n)	HCV genotype	Treatment	Duration, weeks	RVR	ETR	SVR	NR	Relapsers
Aziz et al 2016[8]	Islamabad/ Rawalpindi	921	Predominantly genotype 3a	IFN alfa-2b plus ribavirin	24 weeks		74.8%	60.2%	25.2%	14.66%
Qureshi et al 2014[33]	Islamabad/ Rawalpindi	199	Genotype 3	PEG-IFN alpha-2b 3 million IU thrice weekly plus ribavirin (1000–1200 mg/day)	24 weeks		84.92%	63.31%	15.07%	21.60%
Pervaiz et al 2013[17]	KPK	50	Genotype 3a	IFN-α 2a (180 μg /week) and Ribavirin (400 mg/day) for a total of 24 weeks		4%	60%	60%	40%	0%
Aziz et al 2012[18]	Islamabad/ Rawalpindi	426	HCV genotype 3	PEG-IFN alpha-2a (Pegasys) at the standard dose of 180 mg/ week subcutaneously and ribavirin 800 mg daily	24 weeks	74.6%	89.2%	75.1%	10.8%	14.5%
Gil et al 2013[36]	Islamabad	460	HCV genotype 3	PEG IFN alfa-2a 180 mg/week and ribavirin	16–24 weeks	76.3%	84.5%	74.8%	9.7%	16.5%
Aziz et al 2011[28]	Islamabad	403	HCV genotype 3 (383 patients) and 1a (20 patients)	PEG IFN alfa-2b 3 million IU thrice weekly plus ribavirin (1000–1200 mg/day)	24 weeks	86%	90.3%	74.69%	9.7%	14%
Irfan et al 2011[21]	Lahore	244	Genotype 2 and 3	Conventional interferon and ribavirin provided by PMP Program	24–48 weeks depending on HCV genotype		77.71%	50.955%	22.293%	26.75%
Ahmed et al 2011[22]	Karachi	829	Genotypes 1, 2, 3 and 4	INF 3 MU subcutaneously 3 times per week combined with ribavirin (800–1200 mg/day depending on weight of the patient)	48 weeks for genotypes 1 and 4, and 24 weeks for genotypes 2, 3.		74%	63%	26%	11%
Butt et al 2009[24]	Karachi	66	Genotype 3 patients with cirrhosis with Child Turcotte Pugh (CTP) Class A and B due to genotype 3 HCV infection	50% Patients treated with peg-INFα-2a (180 μg/week) with ribavirin and 50%; Peg-INFα-2b (1 μg/kg/week) with ribavirin	36 to 48 weeks	66.7%	69.7%	57.6%	30.3%	12.1%
Khan and Sarwar, 2009[19]	Lahore	610	HCV infected patients with genotype 2 and 3	Peg-INF + RBV therapy in 73 patients while standard INF + RBV therapy in all the rest of the patients	24–72 weeks depending on the antiviral response to the therapy		84%	72.7%	11.1%	16.1%
Qureshi et al 2009[16]	Islamabad	190	HCV-RNA positive patient with genotype 3a	INFα-2a, 3 MU 3 times/week plus Ribavirin 1000–1200 mg/ day	24 weeks		81.6%	58.95%	18.4%	22.63%
Ali and Iram, 2009[30]	Okara, Kohat, Shorkot and Abbottabad	1000	anti-HCV Positive (ELISA) and HCV-RNA positive patients	INFα-2b, 3 MU 3 times/week for 24 weeks plus Ribavirin 1000–1200 mg/day. For patients with age 5–15 years INFα-2b 50,000 IU/kg body weight plus Ribavirin 15 mg/kg body weight	26 weeks		95%	85.5%	5%	9.5%
Zuberi et al 2008[6]	Karachi	74	HCV-RNA positive patients with genotype 3a	INFα-2a, 3 MU 3 times/week plus Ribavirin 1000–1200 mg/ day	16 weeks for patients with HCV-RNA negative after 4 weeks of treatment, and 24 weeks for the rest of patients	45.9%	70.3%	33.8%	29.7%	36.5%
Mahsud et al 2008[25]	Peshawar	310	Noncirrhotic chronic hepatitis C; adult patients with anti-HCV Positive (ELISA) and HCV-RNA positive	INFα-2b, 3 MU 3 times/week for 24 weeks plus Ribavirin 1000–1200 mg/day	24 weeks	71.62%	81.12%	78.06%	18.9%	3.04%
Farooqi and Farooqi, 2005[63]	Peshawar	65	HCV-RNA positive patients with raised ALT levels	INFα-2b, 3 MU 3 times/week for 24 weeks plus Ribavirin 1200 mg/day	24 weeks		86.15%	83.1%	13.9%	3%
Muhammad et al 2004[27]	District Buner	350	Noncirrhotic, chronic hepatitis C patients with anti-HCV antibodies (ELISA) and HCV-RNA positive	INFα-2b, 3 MU 3 times/week plus Ribavirin 1000–1200 mg/ day	24 weeks	78.5%	85.14%	78.85%	14.86%	6.29%
Hussain et al 2004[20]	Rawalpindi	229	HCV-RNA positive patients	INFα-2b, 3 MU 3 times/week plus Ribavirin 800–1200 mg/ day	24 or 48 weeks		86.5%	76%	13.5%	10.5%
Khokhar, 2002[9]	Islamabad	98	Chronic hepatitis C patients	INFα-2b, 3 MU 3 times/week plus Ribavirin 800–1200 mg/ day	48 weeks		83%	79.5%	17%	3.5%

ELISA = enzyme linked immunosorbent assay, ETR = end of treatment response, HCV = hepatitis C virus, IFN = interferon, MU = million international units, NR = nonresponders, RBV = ribavirin, RVR = rapid virological response, SVR = sustained virological response.

Table 2

Retrospective studies describing treatment response rates to INF + RBV therapy in Pakistani HCV infected population.

Author	Region	Etiology	Patients (n)	Treatment	Duration, weeks	RVR	ETR	SVR	NR	Relapsers	Results
Akram et al 2011[29]	Lahore	Patients with chronic HCV infection, anti-HCV ELISA and serum HCV; RNA positive	86	INF 3 MU 3 times/week and Ribavirin 10 mg/day/kg of body weight	24–48 weeks depending on the type of the genotype	4.7%	69%	53.5%	30.2%	16.3%	Male patients were observed with higher SVR values
			50	Peg-INF (80 MU/mL once a week) and Ribavirin 10 mg/day/kg of body weight	12–72 weeks	2%	80%	70%	20%	10%	
Aziz et al 2011[28]	Islamabad	HCV-RNA positive patients with genotype 3 infections	383	PEG-IFN-α-2b (1.5 mg/kg/week/ body weight) plus ribavirin 800–1000 mg/day	24 weeks for HCV genotype 3	76.2%	90.3%	76%	24%		RVR is favorable marker for SVR in HCV infected patients
Aziz et al 2010[15]	Karachi	HCV-RNA positive with genotype 3 infection	155	INF-α 2a 3 MU 3 times/week and Ribavirin 1000–1200 mg/day	24 weeks		83.8%	87.1%*	16.2%		Almost similar values for ETR and EVR were observed with both INF-α 2a and INF-α 2b. However, the later was associated with more side effects
			155	INF-α 2b 3 MU 3 times/week and Ribavirin 1000–1200 mg/day	24 weeks		83.2%	83.3%*	16.8%		
Idrees and Riazuddin, 2009[3]	4 provinces	HCV-RNA positive with genotype 1	70	INF-α 2b 3 MU 3 times/week and Ribavirin 1000–1200 mg/day	48 weeks		40%	24.3%	60%	15.7%	RVR, low pretreatment viral load, HCV genotypes 2 & 3, age < =40 years and ethnic group; Pashtoon appear to have the highest probability of ETR and SVR
		HCV-RNA positive with genotype 2	33		24 weeks		84.8%	69.7%	15.2%	15.1%	
		HCV-RNA positive with genotype 3	260		24 weeks		75%	57.3%	25%	17.7%	
		HCV-RNA positive with genotype 4, 5a and 6a	6		48 weeks for HCV 4, 24 weeks for HCV 5a & 6a		66.7%	50%	33.3%	16.7%	
		HCV-RNA positive with mixed genotype infection	31		48 weeks		41.9%	32.3%	58.1%	9.6%	
Khalid et al 2009[32]	Lahore	Treatment naïve chronic hepatitis C patients with positive HCV-RNA (HCV-3a)	8	INFα-2b, 5 MU/day for 2 weeks followed by 3 MU thrice weekly for the next 22 weeks plus Ribavirin 1200 mg/day	24 weeks		88%	62.5%	12%	25.5	Treatment with INFα-2b, 5 MU/day for 2 weeks followed by 3 MU thrice weekly for the next 22 weeks plus Ribavirin 1200 mg/ day was found more effective
			8	INFα-2b, 3 MU 3 times/week plus Ribavirin 1000–1200 mg/day	24 weeks		62.5%	50%	37.5	12.5%	
Shaikh et al 2002[23]	Larkana	Patients with HCV-RNA positive biopsy proven chronic liver disease and raised serum ALT for 6 months	40	INF, 3 MU 3 times/week	24 weeks		47.5%	27.5%	52.5	20%	Combination therapy of INF and ribavirin is more effective than INF alone
			42	INF 3 MU 3 times/week plus Ribavirin 1000–1200 mg/day	24 weeks		83.8%	71.4%	16.2	12.4%	

ELISA = enzyme linked immunosorbent assay, ETR = end of treatment response, IFN = interferon, MU = million international units, NR = nonresponders, RBV = ribavirin, RVR = rapid virological response, SVR = sustained virological response.

Table 3

Summary of the reports based on the type of antiviral therapy.

Therapy type	Mean %SVR	Number of studies	Std. deviation	Minimum	Maximum
Standard IFN	27.5000	1	–	27.50	27.50
Standard IFN plus RBV	68.3850	21	14.13057	33.80	87.10
PEG-IFN plus RBV	64.3820	5	8.68485	55.00	76.00
Both options depending on genotype	72.7000	1	–	72.70	72.70
Total	66.3641	28	14.84629	27.50	87.10

IFN = interferon, RBV = ribavirin, SVR = sustained virological response.

antiviral therapy due to severe side effects. Most important adverse effects that lead to treatment cessation are shown in Table 4. The most frequent side-effects of antiviral therapy were fever, anemia, vomiting, nausea, anorexia,[43] musculoskeletal pain, headache, fatigue, insomnia[15] however; the treatment was still well-tolerated by most of the patients.[43] Ahmed and co-workers[44] observed seizures in 0.16% (8/4913) of the patients receiving INF + RBV combination therapy. Shaikh et al[23] reported neutropenia in 36% and thrombocytopenia in 28% patients receiving INF +RBV combination therapy. Aziz et al[15] reported that the adverse effects were more severe in the first few weeks of the start of therapy and gradually decreased in intensity as the treatment proceeded. Idrees and Riazuddin[3] reported that 3.75% patients with reduced hemoglobin levels, thrombocytopenia and leucopenia were treated with adjusted doses of INF and RBV. In another study, 7.6% (5/66) were found with adverse side-effects like myalgias, cytopenias and intense lethargy due to antiviral therapy and were treated with reduced doses of INF and RBV.[23] Nadeem et al[34] reported that none of the 107 patients in Rawalpindi discontinued treatment due to side effects. A high frequency of depression (24%–70%) has been reported in patients with HCV infection which varies during INF treatment (0%–82%) depending on the treatment criteria.[45]

Aamir et al[46] studied the cutaneous complications in Pakistani HCV infected population during INF and RBV combination therapy and reported that most (97%) of the patients were observed with cutaneous side effects like hair loss (64%), oral pigmentation (48%), generalized pigmentation (27%), trichomegaly (32%), synophyrs (30%), pruritus (23%), aphthous stomatitis (21%), melasma (18.4%), nail pigmentation (16.8%), urticaria (16.8%) and photosensitivity (3.4%). Although, these undesirable effects were not so severe to discontinue the antiviral therapy however, this information will help dermatologists and physicians to counsel patients during antiviral therapy.

Mahmood and Muhammad[47] studied 400 patients with chronic hepatitis C and reported side effects of INF plus RBV therapy in these patients. The most frequent was hematological side effects reported in 92.5% patients, flu-like symptoms (91%), gastro-intestinal (88.5%), dermatological (81.5%), neuropsychiatric (71.25%), respiratory related side effects (14%), thyroid function abnormalities (4%), major depression (1%), and suicidal tendency (0.5%). In another study, Alam et al[48] reported 2 patients with digital clubbing; an unusual side effect of INF-α therapy however, no other data supporting this hypothesis is available in literature.

3.6. Supportive therapies used in Pakistan

Wazir et al[49] supplemented the INF plus RBV therapy with oral administration of Vitamin E (600 mg 2 times daily) and reported decreased progression of fibrosis in chronic HCV patients. To treat severe anemia caused by the INF+RBV combination therapy, Abbas et al[43] observed that erythropoietin supportive therapy for short period was beneficial. The flu like symptoms exhibited as a result of the antiviral therapy have been treated

Table 4

Proportion of the patients with treatment cessation due to severe side effects of INF + RBV combination therapy.

Author	Region	Total patients	%, Treatment discontinued	Main causes for the treatment discontinuation
Ahmed et al 2011[22]	Karachi	829	1.69% (14/829)	Thrombocytopenia, ascites, depression, arthralgia, weight loss, rashes, fever, loss of hair, and epistaxis
Aziz et al 2010[15]	Karachi	310	3.22% (10/310)	Depression
Ali et al 2010[64]	All regions of Pakistan	116	5.2% (6/116)	Depression, neutropenia, hyperthyroidism
Khalid et al 2009[32]	Lahore	16	6025% (1/16)	Suicidal tendency
Idrees and Riazuddin, 2009[3]	4 provinces	400	1.5% (6/400)	–
Khan and Sarwar, 2009[19]	Lahore	721	1.7% (12/721)	Extreme weakness, severe; Depression, thyroid dysfunction, and leucopenia
Butt et al 2009[24]	Karachi	66	7.57% (5/66)	Cytopenias and poor tolerance to the therapy
Qureshi et al 2009[16]	Islamabad	197	3.55% (7/197)	–
Ali and Iram, 2009[30]	Okara, Kohat, Shorkot and Abbottabad	1000	3% (30/1000)	Patients not responding to erythropoietin and G-CSF supportive therapy
Mahsud et al 2008[25]	Peshawar	310	0.96% (3/310)	decreased hemoglobin and neutropenia
Nadeem et al 2007[34]	Rawalpindi	107	0% (0/107)	–
Muhammad et al 2004[27]	District Buner	350	4.28% (15/350)	–
Khokhar, 2002[9]	Islamabad	98	2% (2/98)	Treatment was tolerable
Total	–	4520	2.45% (111/4520)	–

G-CSF = granulocyte-colony stimulating factor, INF = interferon, RBV = ribavirin.

with simple analgesics like paracetamol.[47] Aziz et al[15] recommended analgesics and antidepressants (after psychiatric consultation) in patients with severe side-effects. Granulocyte colony stimulating factor or erythropoietins were administered as supportive therapy to relief neutropenia and anemia resulting from antiviral therapy.[24] Antiemetics, antiulcers, and blood transfusion can also be beneficial as supportive therapy for the continuation of the anti-HCV treatment to obtain better results.[30]

3.7. Treatment response rates and its association with geographic and ethnic differences

Significant correlation has been reported between ethnicity of the patient and treatment response rates to anti-HCV therapy.[28] Maximum treatment response rates with >78% SVR has been reported in the HCV patients from Khyber Pakhtunkhwa; the north-west province of Pakistan.[25–28] These results further suggest that treatment response rate in Pashtun ethnic group is higher significantly as compared to non-Pashtun HCV infected population. This difference in SVR rates could be due to the difference in host genetic factors.[50] Percent SVR rates to Pegylated INF plus RBV therapy in HCV infected patients residing in Lahore, Punjab (the central Pakistan) has been reported 70%,[29] 74.44% at Islamabad-Capital territory[28] and 57.6% at Karachi-Sindh[24] which shows that treatment response rates differs greatly with the geographical and ethnic groups. The difference in treatment response rates may be due to various host related factors, distribution of different HCV genotypes and quasispecies in different geographic regions of Pakistan.

3.8. Host genetic factors associated with HCV in Pakistan

Beside viral genotype, virological responses after standard treatment and several basic host related factors (gender, age, body mass index, degree of hepatic steatosis and fibrosis), genetic

Table 5

Summaries of the studies conducted on Host genetic factors associated with HCV infection in Pakistan.

References	Region	Patients	Genotypes	Genes	SNPs	Conclusion
Khubaib et al 2015[65]	Lahore	200	3a,1a,1b	*IL28B*	rs12979860	The CC genotype of *IL-28B* SNP rs1297986 is an independent factor for SVR in Chronic HCV
Azam et al 2015[66]	Sindh/KPK	118	3	*TRAIL-R1*	rs4242392	TRAIL-R1 genetic variation rs4242392 might possess a role in interferon-based therapy for chronic HCV patients, while the IFN-c gene SNP rs2069707 is likely to contribute in HCV clearance
				Interferon γ	rs2069707	
Imran et al 2015[67]	Islamabad/KPK	186	3a	*IL28B*	rs12979860	HCV genotype and IL28B rs1297986 are predictive markers for the efficiency of IFN plus ribavirin Co mbinational therapy of HCV infection
					rs8099917	
Reshma et al 2015[68]	Sindh	66	3a,3b,1a,1b	*IL28B*	rs12979860	HCV patients having high IL-28B levels will show no response to interferon therapy compared to those having low levels of IL-28B
					rs8099917	
Shaikah et al 2015[69]	Sindh	220	3a,2a	*IL28B*	rs12979860	IL28B gene polymorphisms have association with HCV treatment response in Pakistani patients and that there was no association between the IL28B gene polymorphisms and severity of liver fibrosis
					rs8099917	
					rs12980275	
Tipu et al 2014[70]	Punjab	150	3a	IFN-λ	rs8109886, rs688187, rs7248668 rs8113007, rs4803217, rs12972991	These SNPs where found to be most suitable for pre diction of treatment. Most significant alleles were.rs8109886, rs8113007 and rs12979860
					rs12979860, rs8105790, rs4803221	
					rs11665818, rs955155, rs8099917, rs8109886,	
Aziz et al 2014[71]	Islamabad	150	3	*IL28B*	rs8099917	IL28B polymorphism is highly associated with SVR to therapy in HCV infected patients
					rs12979860	
Imran et al 2014[72]	KPK	140	3a,3b,1a,1b	*OAS1*	SNP at SAS	SNP at exon 7 SAS of *OAS1* was significantly associated with response to therapy of HCV infection
Hashmi et al 2014[73]	Islamabad	219	3a	*IL28B*	rs12979860	CC genotype is providing protection against HCV infection but once infected the CC genotype patient shows viral persistence following IFN therapy
Imran et al 2014[74]	Sindh/KPK	140	3a,3b,1a,1b	*IL-18*	-607-*137*[*]	No important association was found between TGF-β and GALNT8 genotypes and treatment response of HCV infection. IL-18-607AA and OPN-442TT genotypes can be used as positive predictive markers of interferon plus ribavirin treatment of HCV infection in the Pakistani population
				OPN TGF-β GALNT8	*442*[*]	
					- rs10849138	
Abbas et al 2005[75]	Sindh	40	3a	*IL-10*	-1082-819 -592[*]	There is no significant correlation between cytokine polymorphism and HAI[†] except for the polymorphisms of anti-inflammatory cytokine IL-10, which may influence hepatic inflammatory activity and fibrosis in chronic HCV genotype 3a patients
				IFN-λ	-874[*]	
				TGF-α	-308[*]	
				IL-1 β	-	
				TGF-β	-10[*]	

HCV = hepatitis C virus, IL = interleukin, KPK = Khyber Pakhtunkhwa, TGF-β = transforming growth factor, TRAIL = tumor necrosis factor-related apoptosis inducing ligand receptor 1.

[*] The number indicates SNP position.

[†] Histological activity index.

makeup of host also play vital role in disease development and determining proper treatment plans. There are number of host genetic factors like single-nucleotide polymorphisms of IFNs, interleukin (IL)28A gene, IL28B gene, IL29 gene, IFN-γ, Tumor necrosis factor-related apoptosis inducing ligand receptor 1, human leukocyte antigens class II genes, cytotoxic T lymphocyte antigen-4, IL-10, IL-18, Mannan binding lecithin, Transforming growth factor, low molecular mass polypeptides 7 and Oligoadenylate synthetase genes which regulates treatment response.[51–55] A few studies published from Pakistan elaborate the importance of these single-nucleotide polymorphisms in treatment response and viral clearance (Table 5). Despite the current successes in genetics involving studies that are opening new era in the field of HCV infection, still there is significant gap for the applications of these discoveries into innovative clinical practices[56] and development of a novel therapeutic strategies.[57]

3.9. Advances in Antiviral therapies and challenges for Pakistani patients

During the last decade, improvements in the understanding of the viral life cycle have resulted in development of direct-acting antivirals (DAAs) [reviewed by Dubuisson and Cosset[58] and Scheel and Rice[59] however, there are still many issues that are associated with HCV treatment. These barriers include high percentage of patients who are unaware of their infection, limited access to therapy, high cost, successful HCV treatment does not eliminate the HCC risk,[60,61] genotypic efficacy and occasional occurrence of resistance-associated variants.[62] The recent clinical licensing of DAAs enables viral cure. However, limited access to therapy and treatment failure in patient subgroups warrants a continuing effort to develop complementary antiviral strategies. Furthermore, once fibrosis is established, curing HCV infection does not eliminate the risk for HCC.[61] It would be interesting to investigate the effectiveness of the recently developed antivirals in Pakistani HCV infected patients, in the current transition phase from IFN + RBV to DAA combinations. However, so far there is no published study in this direction.

4. Conclusions

IFN plus RBV combination therapy continues to be used in Pakistan to treat HCV infection. Recently, emerging HCV variants has been reported in Pakistani HCV patients administered with IFN plus RBV antiviral therapy. However, the pattern of emergence of the antiviral resistant HCV variants in the country is still not known. In the era of rapidly changing antiviral therapies; limited information is available from Pakistan about harder to treat viral variants arising in the country. In addition, there is no study that describes cell culture based HCV resistant mutation arising in Pakistan. The present article encourages further studies on understanding host and viral factors associated with HCV in Pakistan.

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