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

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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% ± 8.88% (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.[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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be genetically different from those (HCV-3a isolates) from the rest of the world. In addition, more recently emerging HCV variants has been reported in Pakistani patients in response to IFN plus RBV antiviral therapy. 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 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. As the current manuscript is a review article, it does not require ethical approval from the institutional ethical
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, relapers, 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, relapers 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.[3,6,8,9,15–33] The mean value for rapid virological response were found 48.18% ± 29.20% (SE 9.73) and treatment relapers 14.21% ± 8.32% (SE 1.66).[3,6,8,9,11–36] 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 65.09%/± 14.94% (SE 4.31).[3,6,8,15–18,24,25,33] In nine studies genotype was not determined; mean SVR rates in these studies were 69.06%/± 17.15% (SE 5.17)[20,23,26,27,29,30,32,34] (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 73.69%/ ± 1.41% (SE 0.995) is reported.[19,23] Only 2 studies included all the different genotypes and reported average SVR rates of 57.51% ± 7.75 (SE 5.48).[32,34] 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 revealed significant association (P<0.005) between HCV-genotype and %SVR rates. In addition, significant association between therapy type and genotype (P=0.011).

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 200–1000mg 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[3,9,15,17–19,23,27,30,32,34] reported an average of 2.45% Pakistani HCV-infected patients discontinued
| Author, Year | Region | Patients (n) | HCV genotype | Treatment Details | Treatment Duration, weeks | RVR | ETR | SVR | NR | Relapsers |
|--------------|--------|--------------|--------------|-------------------|--------------------------|-----|-----|-----|----|------------|
| Aziz et al. 2016 | 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 | 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% |           |
| Pervez et al. 2013 | KPK | 50 | Genotype 3a | Peg-IFN alpha-2a (Pegasys) at the standard dose of 180 mg/week plus ribavirin (800–1200 mg/day) | 24 weeks | 74.6% | 92.2% | 75.1% | 10.6% | 14.5% |
| Aziz et al. 2012 | Rawalpindi | 426 | HCV genotype 3 | Peg-IFN alpha-2a (Pegasys) at the standard dose of 180 mg/week plus ribavirin (800–1200 mg/day) | 24 weeks | 84.92% | 63.31% | 15.07% | 21.60% |           |
| Gol et al. 2013 | Islamabad/Rawalpindi | 460 | HCV genotype 3 | Peg-IFN alpha-2a 180 mg/week and ribavirin 800 mg daily | 24–16 weeks | 71.5% | 84.5% | 74.8% | 9.7% | 16.5% |
| Aziz et al. 2011 | Islamabad/Rawalpindi | 403 | HCV genotype 3 | Peg-IFN alfa-2a 180 mg/week and ribavirin 800 mg daily | 24 weeks | 86% | 86.5% | 74.6% | 9.7% | 16.5% |
| Gil et al. 2013 | Islamabad | 460 | HCV genotype 3 | Peg-IFN alfa-2a 180 mg/week and ribavirin 800 mg daily | 24 weeks | 86% | 86.5% | 74.6% | 9.7% | 16.5% |
| Irfan et al. 2011 | Lahore | 244 | Genotype 2 and 3 | Conventional interferon and ribavirin provided by PMP Program | 24–48 weeks depending on HCV genotype | 77.7% | 50.9% | 22.3% | 26.7% |           |
| Ahmed et al. 2011 | Karachi | 829 | Genotype 1, 2, 3 and 4 | Peg-IFN alpha-2a 3 MU 3 times/week plus ribavirin (800–1200 mg/day) | 24 weeks | 66.7% | 69.7% | 57.6% | 30.3% | 12.1% |
| Butt et al. 2009 | Karachi | 66 | Genotype 3 patients with cirrhosis with Child Turcotte Pugh (CTP) Class A and B due to genotype 3 HCV infection | Peg-IFN + 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% |           |
| Khan and Sarwar, 2009 | Lahore | 610 | HCV infected patients with genotype 2 and 3 | Peg-IFN + 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 | Islamabad | 190 | HCV-RNA positive patient with genotype 3a | Peg-IFN alpha-2a, 3 MU 3 times/week plus ribavirin 1000–1200 mg/day | 24 weeks | 81.6% | 58.95% | 18.4% | 22.63% |           |
| Ali and Iqbal, 2009 | Okara, Kohat, Abbottabad | 1000 | anti-HCV Positive (ELISA) and HCV-RNA positive patients | Peg-IFN alpha-2a, 3 MU 3 times/week for 24 weeks plus Ribavirin 1000–1200 mg/day. | 24 weeks | 78.5% | 85.14% | 78.85% | 14.86% | 6.29% |
| Zuberi et al. 2008 | Karachi | 74 | HCV-RNA positive patients with genotype 3a | Peg-IFN alpha-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 | Peshawar | 310 | Noncirrhotic chronic hepatitis C; adult patients with anti-HCV Positive (ELISA) and HCV-RNA positive | Peg-IFN alpha-2b, 3 MU 3 times/week for 24 weeks plus Ribavirin 1000–1200 mg/day | 24 weeks | 71.62% | 81.12% | 78.86% | 18.9% | 3.04% |
| Farooqi and Farooqi, 2008 | Peshawar | 65 | HCV-RNA positive patients with raised ALT levels | Peg-IFN alpha-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 | District Buner | 350 | Noncirrhotic, chronic hepatitis C patients with anti-HCV antibodies (ELISA) and HCV-RNA positive | Peg-IFN alpha-2b, 3 MU 3 times/week plus ribavirin 1000–1200 mg/day | 24 weeks | 78.95% | 85.4% | 78.95% | 14.86% | 6.29% |
| Hussain et al. 2004 | Rawalpindi | 229 | HCV-RNA positive patients | Peg-IFN alpha-2b, 3 MU 3 times/week plus ribavirin 800–1200 mg/day | 24 or 48 weeks | 86.5% | 78% | 13.5% | 10.5% |           |
| Khokhar, 2002 | Islamabad | 98 | Chronic hepatitis C patients | Peg-IFN alpha-2b, 3 MU 3 times/week plus ribavirin 800–1200 mg/day | 48 weeks | 83% | 79.9% | 17% | 3.5% |           |

ELISA = enzyme linked immunosorbent assay, ETR = end of treatment response, HCV = hepatitis C virus, INF = interferon, MU = million international units, NR = nonresponders, RBV = ribavirin, RVR = rapid virological response, SVR = sustained virological response.
Table 2

| Author et al. | Region | Etiology | Patients (n) | Treatment | Duration, weeks | RVR | ETR | SVR | NR | Relapses | 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 |
| | | | | | | | | | | | | |
| Aziz et al. 2011 [28] | Islamabad | HCV-RNA positive patients with genotype 3 infections | 383 | Peg-INFα-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 a favorable marker for SVR in HCV infected patients |
| Aziz et al. 2010 [15] | Karachi | HCV-RNA positive with genotype 3 infection | 155 | INFα-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 INFα-2a and INFα-2b. However, the later was associated with more side effects |
| | | | | | | | | | | | |
| Idrees and Riazuddin, 2009 [3] | 4 provinces | HCV-RNA positive with genotype 1 | 70 | INFα-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 |
| Khalid et al. 2009 [25] | Lahore | Treatment naive chronic hepatitis C patients with positive HCV-RNA (HCV-3a) | 33 | 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 | 84.8% | 69.7% | 15.2% | 15.1% | | 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 |
| | | | | | | | | | | | |
| Shaikh et al. 2002 [23] | Larkana | Patients with HCV RNA positive biopsy proven chronic liver disease and raised serum ALT for 6 months | 8 | INFα-2b, 3 MU 3 times/week plus Ribavirin 1000–1200 mg/day | 24 weeks | 62.5% | 50% | 37.5 | 12.5% | | Combination therapy of INF and ribavirin is more effective than INF alone |
| | | | | | | | | | | | |

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.
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, musculoskeletal pain, headache, fatigue, insomnia however; the treatment was still well-tolerated by most of the patients. Advice and co-workers observed seizures in 0.16% (8/4913) of the patients receiving INF + RBV combination therapy. Shaikh et al. reported neutropenia in 36% and thrombocytopenia in 28% patients receiving INF + RBV combination therapy. Aziz et al. 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 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 effects like myalgias, cytopenias and intense lethargy due to antiviral therapy and were treated with reduced 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. Nadeem et al. reported 2 patients with digital clubbing; an unusual side effect of the antiviral therapy have been treated as a result of the antiviral therapy.

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  | Karachi            | 829            | 1.69% (14/829)            | Thrombocytopenia, ascites, depression, arthralgia, weight loss, rash, fever, loss of hair, and epistaxis |
| Aziz et al 2010   | Karachi            | 310            | 3.22% (10/310)            | Depression                                                      |
| Ali et al 2010    | All regions of Pakistan | 116   | 5.2% (6/116)              | Depression, neutropenia, hyperthyroidism                        |
| Khalid et al 2009 | Lahore             | 16             | 6.025% (1/16)             | Suicidal tendency                                               |
| Idrees and Riazuddin, 2009 | 4 provinces | 400            | 1.5% (6/400)              | –                                                               |
| Khan and Sanwar, 2009 | Lahore            | 721            | 1.7% (12/721)             | Extreme weakness, severe; Depression, thyroid dysfunction, and leucopenia |
| Butt et al 2009   | Karachi            | 66             | 7.57% (5/66)              | Cytopenias and poor tolerance to the therapy                   |
| Qureshi et al 2009| Islamabad         | 197            | 3.55% (7/197)             | –                                                               |
| Ali and Iram, 2009| Okara, Kohat, Shorkot and Abbottabad | 1000 | 3% (30/1000)             | Patients not responding to erythropoietin and G-CSF supportive therapy |
| Mahsud et al 2009 | Peshawar           | 310            | 0.96% (3/310)             | decreased hemoglobin and neutropenia                            |
| Nadeem et al 2007 | Rawalpindi         | 107            | 0% (0/107)                | –                                                               |
| Muhammad et al 2004 | District Buner   | 350            | 4.28% (15/350)            | –                                                               |
| Khokhar, 2002     | Islamabad         | 98             | 2% (2/98)                 | Treatment was tolerable                                         |
| Total             |                    | 4520           | 2.45% (11/4520)           | –                                                               |

G-CSF = granulocyte-colony stimulating factor, INF = interferon, RBV = ribavirin.
with simple analgesics like paracetamol, Aziz et al 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. Antiemetics, antiulcers, and blood transfusion can also be beneficial as supportive therapy for the continuation of the anti-HCV treatment to obtain better results.

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. Maximum treatment response rates with >78% SVR has been reported in the HCV patients from Khyber Pakhtunkhwa; the north-west province of Pakistan. 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. Percent SVR rates to Pegylated INF plus RBV therapy in HCV infected patients residing in Lahore, Punjab (the central Pakistan) has been reported 70%, 74.44% at Islamabad-Capital territory and 57.6% at Karachi-Sindh 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**

| References | Region | Patients | Genotypes | Genes | SNPs | Conclusion |
|------------|--------|----------|-----------|-------|------|------------|
| Khuwa et al 2016 | Lahore | 200 | 3a,1a,1b | IFN-λ | rs12979660 | The CC genotype of IFN-λ SNP rs12979660 is an independent factor for SVR in Chronic HCV infection in the Pakistani population. |
| Aziz et al 2016 | Sindh | 150 | 3a,3b,1a,1b | TRAIL-R1 | rs3820532 | IL-28B rs12979660 is predictive markers for the efficiency of INF plus ribavirin Co mbinational therapy of HCV infection. |
| Imran et al 2015 | Islamabad | 140 | 3a | IFN-γ | rs2096807, rs12979660 | These SNPs were found to be most suitable for prediction of treatment. Most significant alleles were rs1018866, rs8113007 and rs12979660. |
| Reshma et al 2014 | Sindh | 150 | 3a,3b,1a,1b | OPN | rs999917 | IL28B gene polymorphisms have association with HCV treatment response in Pakistan patients and that there was no association between the IL28B gene polymorphisms and severity of liver fibrosis. |
| Shakhah et al 2015 | Sindh | 200 | 3a,2a | TGF-β | rs999917 | These SNPs were found to be most suitable for pre diction of treatment. Most significant alleles were rs1018866, rs8113007 and rs12979660. |
| Tipu et al 2016 | Punjab | 150 | 3a | IFN-λ | rs999917 | IL28B polymorphism is highly associated with SVR to therapy in HCV infected patients. |
| Aziz et al 2016 | Sindh | 150 | 3a,3b,1a,1b | OPN | rs12979660 | IL28B polymorphism is highly associated with SVR to therapy in HCV infected patients. |
| Imran et al 2016 | KPK | 140 | 3a,3b,1a,1b | TGF-β | rs12979660 | SNP at SAS was significantly associated with response to therapy of HCV infection. |
| Hashmi et al 2016 | Islamabad | 219 | 3a | TGF-β | rs12979660 | CC genotype of TGF-β SNP rs12979660 shows viral persistence following INF therapy. |
| Imran et al 2016 | Sindh | 140 | 3a,3b,1a,1b | OPN | rs12979660 | No important association was found between TGF-β and GALNTB genotypes and treatment response of HCV infection. |
| Abbas et al 2015 | Sindh | 40 | 3a | TGF-β | rs10849138 | 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. |

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

1. The number indicates SNP position.
2. Histological activity index.
infection does not eliminate the risk for HCC.\[61\] It would be
strategies. Furthermore, once access to therapy and treatment failure in patient subgroups
clinical licensing of DAAs enables viral cure. However, limited
developed antivirals in Pakistani HCV infected patients, in the
interesting to investigate the effectiveness of the recently
eliminate the HCC risk,\[60,61\] genotypic ef
occurrence of resistance-associated variants.\[62\] The recent
Scheel and Rice\[59\] however, there are still many issues that are
there is no study that describes cell culture based HCV resistant
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\[19\]

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 country is still not known. In the era of rapidly changing antiviral

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