Recurrence of Hepatitis C Virus after treatment with Pegylated Interferon and Direct Acting Antivirals in Punjab, Pakistan.

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Research

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Abstract

Background Although increased response rates concomitant in hepatitis C virus but relapse after treatment is threatened. Therefore, it is terrible requirement to evaluate the response of Pegylated interferon and direct acting antivirals in Pakistan.

Methods This study conducted at Department of Pathology, Nawaz Sharif Medical College Gujrat, while treatment effects monitored in different Government and Private Hospitals of Punjab, Pakistan from July 2017 to January 2019. Total 973 patients administered the recommended dose that divided in two groups (i) Interferon based therapy (ii) direct acting antivirals (DAAs). Other parameters like ALT and viral load studied.

Results The 374 patients given interferon therapy and 32 of 374 were positive after 24 weeks of treatment. Among these 29 patients have same genotype and recurrence was present. While 3 patients were re-infected with different HCV strains. In case of DAAs, only 27 patients were positive among 558 patients after 2 weeks and only one patient re-infected with different genotype. Early and sustained virologic response noted in DAAs. ALT and viral load decreased faster with DAAs that not achieved after 4 weeks with pegylated interferon.

Conclusion SVR appears in DAAs and recurrence rate was high in interferon-based therapy as compared to DAAs. Therefore, reinfection has implications for correct treatment efficiency and to select optimal strategies for retreatment cases.

Introduction

Hepatitis C virus is global health issue that has infected approximately 71 million people worldwide. It has become the seventh, among leading cause of death throughout the world [8,16]. The international community noted the increased hepatitis mortality rate and United Nations include it in Sustainable Development Aims [13]. Global Health Sector Strategy (GHSS) constituted by World Health Organization (WHO) that have claimed to control viral hepatitis until 2030. If GHSS will succeed then incidence of hepatitis will decreased to 90% and mortality rate at level of 65% till 2030 [17]. Almost 10 million cases of hepatitis C virus are now present in Pakistan [10,12]. Contaminated blood, unsterilized surgical and dental instruments, reuse contaminated needles and shaving from barbers are major routes of hepatitis transmission [15]. Only 1% among all positive hepatitis C virus patients are being treated in Pakistan and mostly are poor people that cannot afford this treatment. There are seven main genotypes and eighty six subtypes throughout the world while 3 is most dominant in Pakistan [7,11]. The interferon and Ribavirin was only the best therapy choice for hepatitis C virus patients from 2000 to 2011 [14]. The vital purpose of antiviral therapy was to achieve the target of RNA lower than detection limit that will reduce the chance of getting hepatocellular carcinoma and cirrhosis. Therapy response was dependent on host along with other factors such as age, function of liver, concentration of viral load and genotypes. Severe adverse effects were noted with use of combination therapy and target response was very limited. The response rate was 63% with interferon and ribavirin treatment while 75% using pegylated interferon and ribavirin therapy [2].

The Association known as Asia Pacific Association that Studied on Liver recommended the drug Sofosbuvir along with Ribavirin for the treatment who are infected by Hepatitis C Virus genotype 3 [9]. The direct antiviral agents (DAAs) therapy has radically increased the rate of sustained virological response (SVR) to greater than 90% in patients that are leaving with chronic Hepatitis C Virus infection. In order to define true treatment efficacy and determined most suitable retreatment for patients whom HCV removed in treatment and got infected with new HCV strain later on. It is highly important to differentiate between virologic relapse and reinfection. As patients immunity is not protecting from reinfection after consequent exposure and it is reported by various studies. The Purpose of this study was to evaluate the rate of relapse after treatment with old and new treatment therapies and comparison of response of these therapies against HCV.

Methods

The designed study included a comprehensive protocol for research at department of Pathology,

Nawaz Sharif Medical College, University of Gujrat. From July 2017 to January 2019, total 973 patients for recurrent treatment of HCV admitted. Blood samples for Liver Function Tests (LFTs), viral load and genotypes collected from various points of Punjab. Only 932 patients continued and completed the treatment while other (41) left the treatment. The patients classified in two groups according to therapy: (i) Interferon based therapy (ii) direct acting antivirals (DAAs) to evaluate their response and rate of recurrence. Sustained and early virological response noted for both groups. Complete follow up for 2 years of all these patients was maintained. Statistical analyses performed for continuous variables reported as mean $\pm$ standard deviation and compared by the chi-Squared test. Effectiveness of DAAs and interferon-based therapy measured using bar chart as appropriate. These analyses performed by using Minitab version 17 and P value less than 0.05 denoted as statistical significance. Furthermore, the difference in distributions of covariates analyzed between DAAs and Interferon (IFN) based therapies.

Results

The Nine hundred and seventy three (973) patients chronically infected with hepatitis C virus infection registered, who were receiving the treatment. While Nine hundred and thirty two (932) patients complete the treatment and 41 were withdraw the treatment during the study period. The patients were divided into two groups depending on type of therapy that include the IFN based treatment and direct acting antivirals (DAAs).

Figure 1: Flow of enrolled patients

The 374 patients complete the pegylated interferon based treatment, while 558 patients were treated with DAAs as shown in Fig. 1.

Treatment response of interferon therapy after 24 weeks

In our study, we administered pegylated interferon treatment to 374 patients out of 932 and noted that there was a detectable HCV RNA in 32 patients after treating until week 24. The end treatment response achieved in 342 cases while only 32 patients showed positive HCV RNA at week 24. Out of 32 patients who received interferon-based treatment, 29 patients had same HCV genotype while three patients have different genotype (Fig. 2).

Figure 2: Response of interferon therapy after 24 weeks of treatment and number of

non responder along with status of genotypes.

Treatment response of DAAs after 2 week

A total number of 558 patients that were treated by using the direct acting antivirals (DAAs) and significant reduction in viral load was noted in first two weeks of treatments. There were only twenty seven patients that have detectable RNA after 2 weeks of treatment. Among these 27 patients, 26 patients were reinfected with same genotype and only one patient was reinfected with different genotype. Early response rate was high in DAAs therapy as shown in Fig. 3.

Figure 3: Response of DAAs after 2 weeks of treatment and number of non-responder

along with status of genotypes.

Effect of DAAs and Interferon based therapies on ALT and Viral load

The effectiveness of DAAs was high as compared to Interferon based therapies, significant reduction in ALT and viral load noted with DAAs after one week that not achieved with interferon based therapies after 4 weeks. Chi-square method with p value=0.000, indicate the treatment efficiency of DAAs and interferon. Early and sustained virological response noted with DAAs that not achieved by using interferon and on other hand less adverse effects noted with DAAs as compared to interferon therapy as shown in Table 1.

Parameters	Before treatment	After 1 week (DAAs)	After 4 weeks (Interferon)	All	Pvalue
ALT	261	83	137	481	0.000
	54.26	17.26	28.48	100.0	
	0.059	0.484	0.097	0.080	
	0.044	0.014	0.023	0.080	
Viral Load (IU/ml)	440500	17050	141370	598920	0.000
	73.55	2.86	23.60	100.0	
	99.94	99.51	99.90	99.92	
All	440761	17133	2.86 141507	599401	0.000
	73.53	100.000	23.61	100.00	
	100.000		100.000	100.000	

(Table 1) Showing the treatment efficiency of DAAs and Interferon on ALT and viral load by Pearson Chi-Square, P-Value = 0.000.

Discussion

The present study was designed to evaluate the recurrence of hepatitis C virus after treatment with Direct Acting Antivirals and interferon based therapy in Punjab, Pakistan. We registered 973 cases of HCV patients and only 932 completed the treatment. The patients divided in two groups that depending on the type of treatment that include interferon based treatment and direct acting antivirals (DAAs). Only 32 patients were unable to clear the virus after treatment with interferon therapies, out of which 29 patients were infected with the same genotype as before treatment while 3 were re-infected with different genotypes. [18] Showed that sustained virological response with DAAs was 85% in HCV genotype 3 infected cases who received therapy for 24 weeks. While [1] concluded the results that DAAs therapy achieved 96.5% early virological response to HCV genotype 3 patients. Our results are much better than these clinical trials. It was shown that the different factors effects the rate of response of interferon based treatment including the age of patient, liver condition, viral load, viral genotype and treatment history [2, 13]. In present study, we analyzed the effects of treatment and their outcomes by using important parameters like ALT and viral load along with duration of treatment. Early virological response was achieved with DAAs in short duration that was not achieved by interferon therapy after long time. In Scandinavian countries, [3] injected DAAs to HCV genotype 3 patients and noted Sustained virological response in cirrhotic and non-cirrhotic patients that was 90% and 100. We have 932 patients under treatment for HCV genotype 3, the 29 cases with same Hepatitis C Virus genotype and 3 with other HCV genotypes in interferon base therapy. While 558 treated with DAAs and only 27 did not achieved early virological response. Among these 27 patients, 26 re-infected with the same genotype while only one re-infected with different genotype. Sofosbuvir and Ribavirin therapy showed sustained virological response of 90.4% among hepatitis C virus genotype 2 patients in japan [6]. The viral load is an important indicator for examine of sustained virological response in those who are on Interferon therapy [2]. In our study, a significant reduction in viral load was seen with interferon based therapy and DAAs. The duration of therapy was an important factor in both cases. Early and sustained virological response was present with DAAs as compared to interferon-based therapy and rate of recurrence of HCV infection was high in case of interferon-based therapy as compared to DAAs. As HCV affects the state of liver and other function of liver enzymes that indicate existing form along with liver function. In present research, we analyzed that ALT is an important liver enzyme before and after the treatment to check if there is any change in impact of treatment. The p value was significant for biochemical and molecular parameters. WHO has announced to achieve the target of treating 80% of hepatitis C virus cases until 2030 [17]. So, it is highly needed to evaluate those patients that have chronic HCV and to admit all these patients in treatment program. The price of drug is main treatment hurdle in many Countries [4]. Pakistan is placed at 149 out of 188 countries are trying towards sustained developmental goals in health related issues [5]. Presently, the People of Pakistan are living at second highest load of hepatitis C virus among the entire world. The present treatment response is 1% and all efforts of government for treatment of HCV patients are negligible instead of such high alarming situation as more than 10 million patients are infected. Many treatments centers are still using the interferon-based therapy instead of DAAs, as price is the main concern. There is terrible requirement to provide the DAAs in hepatitis control and treatment programs.

Conclusions

Our study concluded that early and sustained virological response appears in DAAs as compared interferon based therapy. The rate of recurrence was high in interferon-based therapy as compared to DAAs and high reduction in liver enzyme and viral load noted in DAAs as

compared to interferon. This study emphasize on use of DAAs in every health sector working on treatment of Hepatitis C virus and less use of interferon. Therefore, reinfection require correct treatment efficiency and to select optimal strategies for retreatment cases.

Abbreviations

HCV

SVR

DAAs

ALT

GHSS

WHO

RNA

LFTs

IFN

Declarations

i) Ethical Approval

Our Study was conducted under routine cases of patients who were taking the therapies as per their schedule. We did not conduct any animal trails or additional human trials for which we have to apply for any kind of approval. Ethical approval did not apply to our study.

ii) Consent to Publication

Our manuscript did not contain data that requires any kind of consent.

iii) Availability of Data

We do not wish to share our data, as this is part of (PhD) student thesis work that is under publication process. We can provide in future when this whole research will be published.

iv) Competing Interests

There is no conflict of interest.

v) Funding

There is no Government or Private organization financially supporting to this research. All funds are paid by authors themselves and all necessary documentations/publication fees etc. will be paid from the pocket of authors.

vi) Authors Contributions

MUHAMMAD NAEEM RAZA (First and Corresponding author) held this research work including the collection of sample, designing of analysis, experimental work and writing paper. Dr. Kalsoom Sughra and Dr. Nadia Zeeshan help and assist in optimization of research methodologies and other trouble shooting in this work as per their expertise. All authors contributed in this research work.

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References

- [1] Akhtar ST, Umar M, Khaar H, Aslam F, Nisar G, Naseer A, Ahmad S, Osama M. 2016. Sofosbuvir for the treatment of hepatitis C genotype 3 infected patients in Pakistan. *JAMC* **28**(4Supp I1):S884_S889.
- [2] Aziz H, Raza A, Waheed Y, Gill U, Gil ML. 2012. Analysis of variables and interactions among variables associated with a sustained virological response to pegylated interferon alpha 2a plus ribavirin in hepatitis C virus genotype 3 infected patients. *International Journal of Infectious Diseases* **16**(8):e597_602 (DOI 10.1016/j.ijid.2012.03.012).
- [3] Dalgard O, Weiland O, Noraberg G, Karlsen L, Heggelund L. 2017. Sofosbuvir based treatment of chronic hepatitis C genotype 3 infections-A Scandinavian real-life study. *PLOS ONE* **12**(7):e0179764 (DOI 10.1371/journal.pone.0179764).
- [4] Hill A, Simmons B, Gotham D, Fortunak J. 2016. Rapid reduction in prices for generic Sofosbuvir and Daclatasvir to treat hepatitis C. *Journal of Virus Eradication* **2**(1):28_31.
- [5] Ilyas F. 2016. Pakistan ranked 149th in UN health goals. Dawn. 23 September, 2016. Available at <https://www.dawn.com/news/1285528>.
- [6] Kanda T, Nakamura M, Yasui S, Haga Y, Tawada A. 2017. Treatment of Real-World HCV genotype 2 infected Japanese patients with Sofosbuvir plus Ribavirin. *Biology* **6**(2):Article 30.
- [7] Messina JP, Humphreys I, Flaxman A, Brown A, Cooke GS, Pybus OG, Barnes E. 2015. Global distribution and prevalence of hepatitis C virus genotypes. *Hepatology* **61**(1):77_87 (DOI 10.1002/hep.27259).
- [8] Naghavi M, Wang H, Lozano R, Davis A, Liang X. 2015. Global, regional and national age sex specific all cause and cause specific mortality for 240 causes of death, 1990-2013: a systematic analysis for the global burden of diseases study 2013. *Lancet* **385**(9963):117_171 (DOI 10.1016/S0140-6736(14)61682-2).
- [9] Omata M, Kanda T, Wei L, Ming-Lung Y, Chuang WL. 2016. APASL consensus statements and recommendation on treatment of hepatitis C. *Hepatology International* **10**(5):702_726 (DOI 10.1007/s12072-016-9717-6).
- [10] Saeed U, Waheed Y, Ashraf M, Waheed U, Anjum S, Afzal MS. 2015. Estimation of hepatitis B virus, hepatitis C virus, and different clinical parameters in the thalaseemic population of capital twin cities of Pakistan. *Virology: Research and Treatment* **6**:Article 11.

[11] Smith DB, Bukh J, Kuiken C, Muerhoff AS, Rice CM, Stapleton JT, Simmonds P. 2014.

Expanded classification of hepatitis C virus into 7 genotypes and 67 subtypes: updated criteria and genotype assignment web resource. *Hepatology* **59**(1):318_327 (DOI 10.1002/hep.26744).

[12] Waheed Y, Najmi MH, Aziz H, Waheed H, Imran M, Safi SZ. 2017. Prevalence of hepatitis C in people who inject drugs in the cities of Rawalpindi and Islamabad, Pakistan. *Biomedical Reports* **7**(3):263_266 (DOI 10.3892/br.2017.959).

[13] Waheed Y. 2015a. Effect of Interferon plus ribavirin therapy on hepatitis c virus genotype 3 patients from Pakistan: treatment response, side effects and future prospective. *Asian Pacific Journal of Tropical Medicine* **8**(2):85_89 (DOI 10.1016/S1995-7645(14)60193-0).

[14] Waheed Y. 2015b. Transition from millennium development goals to sustainable development goals and hepatitis. *Pathogens and Global Health* **109**(8):353 (DOI 10.1080/20477724.2015.1126035).

[15] Waheed Y, Shafi T, Safi SZ, Qadri I. 2009. Hepatitis C virus in Pakistan: a systematic review of prevalence, genotypes and risk factors. *World Journal of Gastroenterology* **15**(45):5647_5653 (DOI 10.3748/wjg.15.5647).

[16] World Health Organization. 2017. *Global hepatitis report 2017*. Available at <http://apps.who.int/iris/bitstream/handle/10665/255016/9789241565455-eng.pdf;jsessionid=E2D0796013167FC7FFA0295C58EF490D?sequence=1>.

[17] World Health Organization. 2016. Global health sector strategies on viral hepatitis 2016_2021. Available at http://apps.who.int/gb/ebwha/pdf_files/WHA69/A69_32-en.pdf?ua=1.

[18] Zeuzem S, Dusheiko GM, Salupere R, Mangia A, Flisiak R. 2014. Sofosbuvir and Ribavirin in HCV genotype 2 and 3. *New England Journal of Medicine* **370**(21):1993_2001 (DOI 10.1056/NEJMoa1316145).

Figures

Figure 1

Flow of enrolled patients

Figure 2: Response of interferon therapy after 24 weeks of treatment and number of non responder along with status of genotypes.

Figure 2

Response of interferon therapy after 24 weeks of treatment and number of non responder along with status of genotypes.

Figure 3: Response of DAAs after 2 weeks of treatment and number of non-responder along with status of genotypes.

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