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# COMPARISON OF HCV TREATMENT;
## HCV MONO-INFECTED AND HCV/HBV CO-INFECTED PATIENTS.

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**ABSTRACT… Objectives:** To analyze End of Treatment Response (ETR) and Sustained Virological Response (SVR) to HCV mono-infection in comparison with HCV/HBV co-infection. **Study Design:** Retrospective, multicenter study. **Place and duration of study:** The study was conducted at Department of Biochemistry and Molecular Biology, Army Medical College in collaboration with Armed Forces Institute of Pathology (AFIP), Rawalpindi and was completed in 12 months. **Material and Methods:** This study included two hundred and twelve HCV infected patients, treated with IFN-α-2b 6MU thrice weekly plus ribavirin 1000-1200 mg daily for 24 weeks duration. The subjects were divided into two groups of 152 HCV mono-infected and 60 HCV/HBV co-infected patients. Pretreatment biochemical factors, EVR and SVR were compared between two groups. **Results:** There is no significant difference between the proportions of HCV mono-infected versus HCV/HBV co-infected patients with ALT & AST levels before interferon therapy. The analysis by intention to treat exhibit EVR of 75% and 60% among co-infected and mono-infected patients respectively ($p = 0.038$). Similarly, SVR of 50% and 45% was observed in HCV/HBV co-infected and mono-infected patients ($p = 0.489$). **Conclusions:** HCV/HBV co-infected and HCV mono-infected patients had similar biochemical characteristics with significant lower HCV-RNA titer in mono-infected patients. HCV/HBV co-infected patients showed higher EVR and SVR rates to interferon-alpha/ribavirin combination therapy as compare to mono-infected patients. The most possible factors responsible for favorable response rate in co-infected patients would be due to positive host immune reaction and reciprocal viral interaction.

**Key words:** HCV mono-infection, HCV/HBV co-infection, End of Treatment Response (ETR), Sustained Virological Response (SVR).

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## INTRODUCTION

Hepatitis C virus represents a major public health issue across the world in general, particularly in Pakistan. HCV co-infection with hepatitis B virus (HBV) has emerged as one of the leading causes of morbidity due to cirrhosis or hepatocellular carcinoma.[1]

Pakistan has a high incidence rate of hepatitis B (2.5%) and hepatitis C (5%) due to highly dense population with general poverty and lack of education.[2] Among HCV infected patients, around 2-3% is co-infected with hepatitis B.[3] Natural course of hepatitis C infection can be accelerated by HBV leading to cirrhosis and hepatocellular carcinoma. However, clinical studies have confirmed that inhibition of HBV activity is mainly exerted by HCV core protein, suggesting high prevalence of HBV suppression in hepatitis C infected patients. There is also a reciprocal inhibitory effect of both viruses during and after antiviral treatment.[4]

Recommended therapy for chronic hepatitis C patients is interferon-alpha plus ribavirin in combination for 48 weeks duration. However, efficacy of interferon-alpha and ribavirin therapy in HCV/HBV co-infected patients is still not clear.[5]

Incidence of developing fulminant and sub-fulminant hepatitis can be affected by several variables such as host factors (age, gender) as

well as hepatic enzymes (ALT, AST) and hepatic serology.[6] A framework has been proposed to analyze various laboratory parameters required for calculation of risks and benefits of therapy suitability, advisability and eligibility. There are modifiable and non-modifiable factors responsible for treatment applicability and therapy benefits in advancement of long-term clinical outcomes of dually infected patients.

## PATIENTS AND METHODS

### Source of data

A case-control study conducted to investigate the response efficacy of interferon-alpha (IFN-alpha) and ribavirin combination therapy. It is a retrospective observational study. This study included 212 diagnosed HCV patients and out of which 60 were co-infected with HBV infection, recruited between August 2012 and June 2014. This study was done at Department of Biochemistry and Molecular Biology, Army Medical College, Rawalpindi in collaboration with Armed Forces Institute of Pathology (AFIP), Rawalpindi. Informed written consent was taken from all patients and approval from Institutional Ethics committee. This study protocol was according to ethical principles of the Helsinki Declaration and approved by Ethics Committee of the Army Medical College, NUST.

### Study Variables

All two hundred and twelve (out of which 152 HCV mono-infected and 60 HCV/HBV co-infected) patients undergone complete interferon-α therapy at the dose of 3MU, three times a day for duration of 48 weeks. Patients were then categorized into group C (HCV mon-infected) and group CB (HCV/HBV co-infected patients). Patients of group C were considered as case control and positive for HCV-RNA and HCV antibodies. Patients of group CB were positive for HCV-RNA, HCV antibodies, HBeAg and HBV-DNA levels ≥ 20,000 IU/ml. The groups were compared regarding their general baseline data, virological response and tolerance to interferon-α therapy. The medical records of all patients were evaluated in their entirety at the time of enrolment. Report form comprises of independent predictors such as (age, gender) and dependent predictors (clinical and biochemical characteristics) of infected patients. Serum HCV-RNA and HBV-DNA levels were analyzed at baseline, at third month of interferon therapy and 6 months after completion of therapy. Patients positive for hepatitis D, HIV infection or autoimmune hepatitis were excluded from this study.

### End-points

Primary end-point includes early virological response (EVR) and sustained virological response (SVR), defined as absence of serum HCV-RNA at third month of interferon therapy and six months after stopping the therapy. Relapse rate was undetectable HCV-RNA at the end of interferon therapy but detectable HCV-RNA levels 6 month after completion of therapy.

### Safety evaluation and visit schedule

Careful follow up of all patients was done at 6-month after completion of therapy. Interferon therapy was discontinued in case of severe adverse effects like platelet count $< 50{,}000/mm^3$.

## RESULTS

The statistical analysis of data was performed on spread sheet of Statistical Package for the Social Sciences (SPSS version 20). Univariate analysis was applied to each variable to determine clinical outcome of each patient. The categorical variables were compared and analyzed by using chi-square and Fisher's exact tests. Noncategorical variables were evaluated by Student's *t* test. Two-tailed *p*-value of less than 0.05 was considered statistically significant.

Two hundred and twelve patients were included and categorized into two groups. Group C comprises of 71.7% (n = 152) HCV mono-infected patients and group CB with 39.47% (n = 60) HCV/HBV co-infected-patients. Table-I demonstrates the pretreatment parameters of both groups. Group C patients showed lower mean age of 35.70 ± 6.7 years than 38.27 ± 8.4 years in group CB patients, which is statistically significant ($p = 0.059$). Analysis of biochemical

factors revealed higher HCV-RNA levels in group C (6.14 ± 0.83) when compared with group CB (5.84 ± 0.84).

Table-II shows different modes related to virological response and patient's tolerance to interferon therapy. The results conclude achievement of higher HCV EVR and lower relapse rate in HCV/HBV co-infected patients than in HCV mono-infected patients (75% vs. 60%, p = 0.038) and (18% vs. 38%, p = 0.006) respectively. Due to interferon-alpha treatment side effects, interruption to therapy was observed in 18% group CB as compare to 32% in group C patients.

| Variable | Group C (n=152) | Group CB (n=60) | *p* value |
|---|---|---|---|
| **Male** | 102 | 39 | 0.770 |
| **Female** | 50 | 21 | |
| **Mean Age (years)** | 35.7 ± 6.7 | 38.27±8.4 | 0.059* |
| **BIOCHEMICAL FACTORS** | | | |
| **AST (IU/L)** | 63.28 ± 22.29 | 69.98 ± 26.01 | 0.062 |
| **ALT (IU/L)** | 64.13 ± 28.25 | 72.22 ± 33.69 | 0.077 |
| **HCV- RNA ($log_{10}$ U/mL)** | 6.14 ± 0.83 | 5.84 ± 0.84 | 0.017* |
| **HBV-DNA ($log_{10}$ IU/mL)** | - | 2.70 ± 0.93 | - |

**Table-I. Univariate analysis of laboratory parameters between group C and CB.**

| Parameters | Total no of patients (N) | Group C (n= 152) | Group BC (n=60) | *p* value |
|---|---|---|---|---|
| **EVR** | 136 | 60% (91) | 75% (45) | 0.038* |
| **Relapse Rate** | 69 | 38% (58) | 18% (11) | 0.006* |
| **SVR** | 98 | 45% (68) | 50% (30) | 0.489 |
| **Interruption due to side effects** | 59 | 32% (48) | 18% (11) | 0.05* |

**Table-II. Comparison of groups related to interferon therapy among two groups.**
* $p \leq 0.05$ (Statistically Significant)

## DISCUSSION

Dual hepatitis C virus and hepatitis B virus infection is common in HCV or HBV endemic areas. However, there's scarce information regarding hepatitis B virus impact on the response to therapy in HCV/HBV co-infected patients. Aims of interferon therapy is to eliminate viral loads, achievement of sustained virological response and to lower recurrence rate of HBV at the end of therapy. Although HCV/HBV co-infection are more likely to develop fulminant hepatitis, the interaction between the HCV and HBV appears to be one of reciprocal inhibition, each averting or greatly reducing the ability of the other virus to replicate. Several studies have suggested that HBV superinfection may reduce the severity of hepatitis C infection as compare to mono-infected patients.

This is a retrospective, multicenter study conducted to identify baseline biochemical parameters, response to therapy and relapse rate of hepatitis C mono-infected patients in comparison with HCV/HBV co-infected patients. A total of 212 Hepatitis C infected patients along with their age, gender, and baseline laboratory parameters were included in the data analysis from January 2009 to February 2014. Patients were divided into two groups: group C (HCV mono-infected) and group CB (HCV/HBV co-infected).

Over the last decade, several studies showed response probability to therapy according to the kinetics of HCV-RNA and HBV-DNA levels. So, most of the patients who failed to achieve early

virological response (EVR), did not achieve SVR.[7]

Our study showed higher EVR rate and lower relapse rate in HCV/HBV co-infected patients than HCV mon-infected patients which is statistically significant ($p = 0.038$ and 0.006 respectively). The most probable possibility is due to enhanced and early immune response induction to interferon therapy.[8,9]

Almost all patients showed mild to moderate side effects to interferon therapy such as flu-like symptoms, diarrhea, depression and bone marrow suppression. However, severe side effects leading to discontinuation of therapy were observed in 48/152 mono-infected patients as compare to 11/60 HCV/HBV co-infected patients, which is statistically significant ($p = 0.05$).

Biochemical analysis showed higher basal level of serum AST and ALT both in mono-infected and co-infected patients.

Our study described a statistically significant difference ($p = 0.017$) between baseline HCV-RNA levels in HCV mono-infected and HCV/HBV co-infected patients. According to previous studies, such finding could be due to a significant lower HCV-RNA levels in the context of HBV co-infection which in turn influence interferon therapy response rate. Also due to enhanced host innate and adaptive immune-mediated response to viruses, there is a complex interaction between HCV and HBV in co-infected patients. Therefore, presence of other viral factors should also be considered before initiation of antiviral therapy. Furthermore, eliminating such factors may result in lower rates of HCV chronicity, lower HCV viremia levels, reduced risk of sexual and vertical transmission, and improved response to HCV therapy.

Further investigations are required for prevention and management of co-infected patients with HBV reactivation receiving peg-interferon therapy. This study had some limitations. We used baseline data and assume that HCV viremia reflects chronic, not recent, infection.

## CONCLUSION

Unfortunately, dual infection represents a therapeutic challenge in developing countries yet poorly understood. As 70% of co-infected patients either shows no response to therapy as nonresponders or experience a relapse after stoppage of treatment as relapsers. In Pakistan, access to treatment for coinfected patients poses a major dilemma due to lack of awareness regarding mode of transmission, poor surveillance systems, expensive diagnostic tests and treatment. A relationship between cellular factors and poor response to IFN-$\alpha$ treatment is required to formulate national health policies and preventive strategies to reduce burden of HCV and HBV coinfection. Moreover, effective interferon-free oral regimens specific against viral and host targets for HCV genotype 3 infected patients are expected to have significant potential for success.



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## AUTHORSHIP AND CONTRIBUTION DECLARATION

| Sr. # | Author-s Full Name | Contribution to the paper | Author=s Signature |
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| 1 | Dr. Maleha Asim | Principal investigator Research conduction | |
| 2 | Dr. Faizania Shabbir | Paper Writing Result compilation & imterpretation | |
| 3 | Dr. Wajeeha Mah Jabeen | Paper Writing Sampling protocol & assistance | |
| 4 | Dr. Kiran-e-Munira | Lab Assays, Result compilation | |
| 5 | Dr. Shakir Khan | Development of sampling protocol | |
| 6 | Dr. Tausif Ahmed Rajput | Result compilation Statistical analysis | |