Original Articles

Effect of induction therapy on Hepatitis C

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ABSTRACT

Objectives: To assess the response to one month induction combination therapy using alpha interferon and Ribavirin on patients with chronic hepatitis C.

Methods: Eighty patients with naive compensated chronic hepatitis C (group A) were followed at King Abdul-Aziz University Hospital, Jeddah, Kingdom of Saudi Arabia from October 1996 through February 2000 received daily subcutaneous injection of alpha interferon - 2b (Intron A 3 million units) plus Ribavirin 1-1.2 grams (induction) for one month followed by Intron A, 3 times a week together with daily Ribavirin (same dose) for 11 months. Response, assessed based on viral load and liver enzymes, was compared to that of 27 patients (group B) who received Intron A 3 million units 3 times weekly and daily Ribavirin (same dose) for 12 months (standard regimen).

Results: A total of 39 patients in group A (48.7%) and 11 patients in-group B (40.7%) had end of treatment response. Twenty nine patients in group A (36.2%) and 5 patients in group B (18.5%) had sustained virologic response. Thirty-seven patients in group A (46.2%) and 6 patients in-group B (22.2%) had sustained biochemical response. None of the patients with cirrhosis in both groups had sustained virologic response. In addition, sustained virologic response in patients with genotype-one and 4 was 31.4% (22 out of 70 patients) in group A and 15.3% (4 out of 26 patients) in group B.

Conclusion: Induction combination therapy improves the sustained biochemical and virologic responses most likely by early prevention of mutation of the virus, which in turn plays a role in the relapse rate.

Keywords: Hepatitis C virus, end treatment response, sustained virologic response.

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Infection with hepatitis C virus (HCV) is a common problem all over the world and it is estimated to affect 170 million people worldwide. This is also true for the Kingdom of Saudi Arabia (KSA) where a prevalence rate of 2.7% among blood donors has been reported.[1] Hepatitis C virus infection is associated with high rate of chronicity with 80% of infected people developing chronic infection with variable rates of progression.[2] Alpha interferon is an established therapeutic agent for treatment of patients with chronic hepatitis secondary to HCV. However, response rate depends on the dose, duration, baseline characteristics and treatment regimen. Monotherapy with alpha-interferon for 6 months achieves a sustained biochemical and virologic response with histological improvement in 7-20%, and 15-30% when treatment is extended for 12-18 months.[3,4] Combination treatment with Interferon and Ribavirin significantly increases the sustained virologic response (SVR) rates. Despite this increased response including in patients with unfavorable virologic demographics such as genotypes one or 4, the response rates remain relatively low.[5-9] Since HCV genotypes in patients in KSA predominantly are genotypes one and 4,[10] and considering what is known regarding HCV kinetics in response to therapy, it was elected to modify the standard combination regimen using one month induction regimen.

Methods. Naive (previously not treated) adult patients (18-60 years) with compensated chronic hepatitis C with the following minimum

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hematological and biochemical criteria: Hemoglobin (Hb) ≥ 12 g/dl for males, ≥ 11 g/dl for females, Leukocyte count (WBC) more than 3,000/mm^3, platelets >100,000/mm^3 normal levels of prothrombin time, bilirubin, albumin, negative hepatitis B surface antigen (HBsAg) and human immunodeficiency virus (HIV) antibody, and abnormal alanine aminotrasferase (ALT) defined as >1.5 upper limit of normal on at least 2 occasions prior to study entry together with no contraindication for using Interferon or Ribavirin. Sexually active females of childbearing potential must be practicing adequate contraception. Upon meeting all eligibility criteria, and after explaining the method of treatment and possible adverse effects of alpha interferon 2b and Ribavirin, patients were enrolled in the study after written agreement. Subcutaneous injection of Intron A (Schering-Plough International) 3 million units (MU) was started daily plus Ribavirin at a dose of 1 - 1.2 g daily (depending on patient's weight) for 4 weeks (induction), followed by Intron A (3 MU) 3 times a week together with Ribavirin (same dose) for 11 months to complete one year therapy (group A). In addition patients who were already started on standard combination regimen (Inton A 3 MU 3 times weekly and daily Ribavirin) in other hospitals, were advised to continue the same regimen to finish 12 months (group B). Ribavirin was given together with Intron A at one gm (<75 kg body weight) or 1.2 gm (> 75 kg body weight) daily in 2 divided doses. Patients included in the study had liver biopsy and the results were classified as cirrhotic or non-cirrhotic. Genotyping and viral load were carried out using branched DNA signal amplification assay (quantiplex branched DNA 2.0 assay, Chiron diagnostics) before treatment and repeat viral load was carried out at the end of one year therapy and 6 months after stopping treatment. Confirmatory qualitative polymerase chain reaction (PCR) (Roche Amplicor monitor test) was carried out for patients having b-DNA level less than 0.2 meq/ml at end or 6 months after treatment. Patients were followed in the clinic monthly with clinical and biochemical assessment until the end of treatment and then every 3 months with liver function test and viral load for 6 months. Statistical Package for Social Sciences (SPSS) was used for analysis. Descriptive statistics were carried out. P-value was set at <0.05 for statistical significance.

Definition of response. Definition of patient response to therapy using end of treatment response (ETR), SVR or sustained biochemical response (SBR) is as follows: End of treatment response - patient who completely normalizes their liver enzymes (alanine aminotransferase [ALT] + aspartate transaminase [AST]) together with quantitative result for viral load using b-DNA of <0.2 meq/ml and negative qualitative PCR at the end of treatment. Sustained virological response -patient who continued to have normal liver enzymes (ALT + AST) together with quantitative result for viral load using B-DNA of <0.2 meq/ml and negative qualitative polymerase chain reaction (PCR) at 6 months after the end of treatment. Sustained biochemical response - patient who continued to have completely normal liver enzymes (ALT + AST) 6 months after the end of treatment irrespective if their viral load.

Results. One hundred and two patients enrolled initially in the study between October 1996 until February 2000 (group A) were followed at King Abdul-Aziz University Hospital, Jeddah, KSA. Nine patients failed to follow up, 7 patients refused to have liver biopsy and 6 patients stopped treatment before completing one year period (one patient developed retinopathy, 3 patients developed severe fatigue, one patient developed excoriating itching, one patient developed dyspnoea with Hb of 9 mg/dl). Thirty patients were included in group B however, 3 patients in this group failed to follow up. Eighty patients completed the study as per scheduled protocol in group A and 27 patients in group B. Forty-nine patients (61.2%) were male, 31 patients (38.8%) were female with age range from 24 to 60 years (mean age 35 years) in group A. Twenty patients (73.3%) were male, 7 patients (26.7%) were female with age range from 26 to 54 years (mean age 40 years) in group B. The patients' response to induction and standard treatment is shown in **Table 1**. Analysis of the response rates based on 3 different variables (presence or absence of cirrhosis, genotypes and viral load) results were as follows:

Histology. Sixty-seven patients (83.7%) in group A and 25 patients (92.5%) in group B had variable degree of inflammation with no cirrhosis while 13 patients (16.3%) in group A and 2 patients (7.5%) in group B had established cirrhosis. In the noncirrhotic group, 29 patients (43.28%) in group A and 5 patients (20%) in group B achieved SVR. In the cirrhotic group only 3 patients (13%) in group A and none in group B had ETR, in addition none in both groups had SVR. Sustained virological response was statistically significant higher in non-cirrhotic patients ($P < 0.05$).

Genotypes. The response to treatment of patients in Group A and B is shown in **Tables 2 & 3**. As most of the studies have shown that genotype 2 and 3 respond better to treatment as compared to genotype 1 and 4,[6,11] patients results were grouped according to their genotype with favourable (2+3) and unfavourable genotypes (1+4). Seventy patients had unfavourable genotype in group A and 26 patients in group B. Ten patients had favourable genotype in group A and one patient in group B. In the unfavourable group, only 31 patients (44.3%) in group A and 10 patients (38.4%) in group B had ETR while 22 patients (31.4%) in group A and 4

Table 1 - Patients' response to induction and standard treatment.

Group	ETR N (%)	SBR N (%)	SVR N (%)
A (80 patients)	39 (48.7)	37 (46.2)	29 (36.2)
B (27 patients)	11 (40.7)	6 (22.2)	5 (18.5)

N - number, ETR - end of treatment, SBR - sustained biochemical response, SVR - sustained virological response.

Table 2 - Group A response.

Genotype	Total N of patients	ETR N (%)	SVR N (%)
1a	10	6 (60)	4 (40)
1b	9	5 (55.5)	4 (44.4)
1a + 1b	3	1 (33.3)	1 (33.3)
2	4	3 (75)	3 (75)
3	6	5 (83.3)	4 (66)
4	43	17 (39.5)	12 (27.9)
1a + 4	5	2 (40)	1 (20)
Total	**80**	**39 (48.7)**	**29 (36.2)**

N - number, ETR - end of treatment response, SVR - sustained virologic response.

Table 3 - Group B response.

Genotype	Total N of patients	ETR N (%)	SVR N (%)
1a	2	2 (100)	1 (50)
1b	8	4 (50)	2 (25)
2	1	1 (100)	1 (100)
4	16	4 (25)	1 (6.2)
Total	**27**	**11 (40.7)**	**5 (18.5)**

N - number, ETR- end of treatment response, SVR - sustained virologic response.

patients (15.3%) in group B had SVR (p=0.09). Eight patients (80%) with the favourable genotypes in group A had ETR and 7 patients had SVR (70%) and the only genotype 2 in group B had both ETR and SVR. Patients with genotype 2 and 3 had statistically significant higher response rate in both groups ($p<0.05$).

Viral load. This was only applied for patients in group A since different methods and units was used for viral load measurement in group B. Patients were grouped according to viral load level into 2 different groups, one group having viral load <1 meq/ml and another having viral load > 1meq/ml. Twenty-three patients were in the low group and 57 patients in the high group. Twelve patients (52.1%) in the low group had SVR as compared to 17 patients (29.8%) in the high group. Though there was higher response rate in the low viral load group, it was not statistically significant (p=0.07).

Discussion. Treatment of chronic hepatitis C infection has been a subject of different studies in the last few years. Initially, treatment with alpha-interferon monotherapy was associated with significant relapses after treatment. Subsequently, studies using combination treatment with alpha-interferon (3 x week) together with daily Ribavirin (standard regimen) demonstrated higher proportion of patients with normalization of liver enzymes, and loss of HCV RNA as detected by PCR together with reduced relapse rates as well. This has been proven in several randomized controlled trails comparing Interferon monotherapy to Interferon and Ribavirin.[3,5] Several factors have shown to influence response rate to combination therapy including host and viral factors, where genotype one is associated with 29% SVR, as compared to 62% for genotype 2 and 3.[5,6,11] In KSA, the most common HCV genotype is genotypes one and 4.[2] Several studies have shown poor treatment response of genotype 4 with SVR less than 20%.[8,9] In this study, 36.25% had SVR in the induction group and 18.5% in the standard regimen group (p=0.054). The majority of patients included (89.9%) had genotypes one and 4. Histology results as well as Hepatitis C virus genotype, were the major variables that influenced the patients response to treatment. Forty percent of patients with no cirrhosis with induction therapy and 20% with standard therapy had SVR as compared to 0% in patients with cirrhosis in both groups. Alternately, 31.4% with genotype one or 4 in the induction group and 15.3% in the standard group had SVR as compared to 70% with genotype 2 or 3 in the induction group. Viral load and sex of the patients in this study did not influence the response rate while young patients (<40 years) had a slightly better SVR (p=0.057). Studies on viral kinetics in patients receiving alpha interferon 3 times weekly showed an intermittent increase in viral load on the treatment free days. This response is

related to interferon short half life (3-8 hours). Single dose Interferon 3 MU subcutaneously results in fluctuating pattern of viral response with decrease in viral titre in 24 hours. Viral titres rebound towards pre-treatment level 36-48 hours after the initial dose.[12] Hepatitis C virus is known to mutate with the development of quasispecies, which plays a major role in resistance of the virus to the treatment as well as high relapse rate. Early clearance of the virus results in better rate of sustained virologic response. The studies of HCV kinetics after initiation of interferon monotherapy showed a rapid dose dependent (3<5<10 = 15 MU) reduction in HCV RNA levels within 24 to 48 hours. This rapid decrease in the viral load is followed by slower phase which is immune-mediated and is variable among different patients depending on death rate of infected cells which is probably the best viral kinetics predictor of early viral clearance.[13,14] Considering interferon half life and estimated viral production rate of 1.0 x 10^{12} virons/day; initial daily interferon treatment probably leads to rapid and higher decline in viral load together with less chance of rebound increase in viral level, viral mutation and hence, higher chance of ETR and SVR which probably explains the difference in response between standard and induction therapy especially in patients with genotypes one and 4 with no liver cirrhosis.

In conclusion, induction combination therapy with Alpha interferon and Ribavirin showed promising results among patients with chronic hepatitis C. However, the optimal induction duration as well as initial interferon dose is yet to be determined. More studies with larger number of patients are needed to confirm the additional response in future or the use of long-acting interferon (Pegylated interferon).

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References

1. Shobokshi OA. Overview of viral hepatitis A through TT virus. *Saudi Journal of Gastroenterology* 2000; 6: 102-103.
2. Alter MJ, Margolis HS, Krawczynski K, Judson FN, Mares A, Alexander WJ et al. The natural history of community acquired hepatitis C in the USA. *N Engl J Med* 1992; 327: 1899-1905.
3. Poynard T, Leroy V, Cohard M, Thevenot T, Mathurin P,Opolon P et al. Metanalysis of interferon randomized trials in the treatment of viral hepatitis: Effects of dose and duration. *Hepatology* 1996; 24: 778-789.
4. Lin R, Roach E, Zimmerman N, Strasser S, Farrell GC. Interferon Alfa-2b for chronic hepatitis C effects of dose increment and duration of treatment on response rates. Results of first multicenter Australian trial. *J Hepatol* 1995; 23: 487-496.
5. McHutchison JG, Gordon SC, Schiff ER, Shiffman ML, Lee WM, Rustgi VK et al. Interferon alfa-2b alone or in combination with Ribavirin as initial treatment for chronic hepatitis C. *N Engl J Med* 1998; 339: 1485-1492.
6. Poynard T, Marcellin P, Lee SS, Niederau C, Minuk GS, Ideo G et al. Randomized trial of interferon-alpha 2b plus Ribavirin for 48 weeks or for 24 weeks versus interferon-alpha 2b plus placebo for 48 weeks for treatment of chronic infection with hepatitis C virus. *Lancet* 1998; 352: 1426-1432.
7. El-Zayadi A, Simmonds P, Dabbous H, Prescott L, Selim O, Ahdy A. Response to interferon alpha of Egyptian patients infected with hepatitis C virus genotype 4. *J Viral Hepat* 1996; 3: 261-264.
8. Al-Faleh FZ, Sbeih F, Al-Karawi M, Al-Mofleh IA, Al-Rashed RS, Ayoola A et al. Treatment of chronic hepatitis C genotype 4 with alpha-interferon in Saudi Arabia: A multicenter study. *Hepatogastroenterology* 1998; 45: 488-491.
9. El-Zayadi A, Selim O, Haddad S, Simmonds P, Hamdy H, Badran HM et al. Combination treatment of interferon alpha-2b and Ribavirin in comparison to interferon monotherapy in treatment of chronic hepatitis C genotype 4 patients. *Ital J Gastroenterol Hepatol* 1999; 31: 472-475.
10. Shobokshi OA, Serebour FE, Skakni L, Al Saffy YH, Ahdal MN. Hepatitis C genotypes and subtypes in Saudi Arabia. *J Med Virol* 1999; 58: 44-48.
11. Martinot-Peignoux M, Marcellin P, Pouteau M, Castelnau C, Boyer N, Poliquin M et al. Pre-treatment serum hepatitis C virus RNA and genotype are the main and independent prognostic factors of SR to interferon alpha therapy in chronic hepatitis C. *Hepatology* 1995; 22: 1050-1056.
12. Perelson AS, Neumann AU, Markowitz M, Leonard JM, Ho DD. HIV-1 dynamics in vivo: Virion clearance rate, infected cell life span, and viral generation time. *Science* 1996; 271: 1582-1586.
13. Lam NP, Neumann AU, Gretch DR, Wiley TE, Perelson AS, Layden TJ. Dose-dependant acute clearance of hepatitis C genotype 1 virus with interferon alpha. *Hepatology* 1997; 26: 226-331.
14. Neumann AU, Lam NP, Dahari H, Gretch DR, Wiley TE, Layden TJ et al. Hepatitis C viral dynamics in vivo and the efficacy of interferon alfa therapy. *Science* 1998; 282: 103-107.