

Treatment of patients with chronic Hepatitis C with normal liver enzymes

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ABSTRACT

Objective: This is a controlled prospective study to evaluate the efficacy of induction combination therapy using alpha-interferon and ribavirin in patients with chronic hepatitis C and persistently normal liver enzymes.

Methods: Forty-six patients with compensated liver disease tested positive for hepatitis C virus antibody between October 1998 and August 2000 at King Abdulaziz University Hospital and Al-Badriyah Towers, Jeddah Clinics, Jeddah, Kingdom of Saudi Arabia. Twelve patients had persistently normal liver enzymes for 6 months and 34 patients with abnormal liver enzymes (control). Patients were treated using induction combination therapy. Viral load response was measured using branched deoxyribonucleic acid signal amplification test.

Results: Ten patients with normal liver enzymes (Group A) and 30 patients with abnormal liver enzymes (Group

B) were included. End of treatment response in Group A was 90% as compared to 60% in group B; sustained virologic response in group A was 40% as compared to 43.3% in Group B.

Conclusion: Response rate to induction combination therapy with alpha-interferon and ribavirin in patients with normal liver enzymes was similar to that in those with increase liver enzymes.

Keywords: Branched deoxyribonucleic acid signal amplification test, end of treatment response, sustained virological response, hepatitis C virus antibody, polymerase chain reaction.

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Patients with persistently normal liver enzymes with hepatitis C represent a unique group. In the United States of America (USA), among blood donors tested positive for hepatitis C virus antibody (HCV-Ab), 27-59% have normal serum alanine aminotransferase (ALT) levels. In addition, among patients tested positive for HCV-Ab with normal serum aminotransferase levels, 54-65% had positive HCV-ribonucleic acid (RNA) detected by polymerase chain reaction (PCR) and hence an estimate of 25% of patients with chronic hepatitis C

have normal liver enzymes.¹⁻³ The prevalence of HCV among Saudi male blood donors is 2.7% (27907 out of 1017303).⁴ The percentage of patients tested positive for HCV-Ab and normal liver enzymes in the Kingdom of Saudi Arabia (KSA) is not known. Treatment of these patients in several uncontrolled trials has been disappointing with current consensus that these patients, considering the mild nature of the disease, are better to be followed up rather than treated.¹

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Methods. Between October 1998 and August 2000, 46 consecutive patients with compensated chronic hepatitis C followed at King Abdulaziz University Hospital (KAUH) and Al-Badriyah Towers-Jeddah Clinics, Jeddah, KSA were included. There were 12 patients with persistently normal liver enzymes for more than 6 months and 34 patients with abnormal liver enzymes (aspartate and alanine transaminases [AST, ALT]). Patients included in the study were tested positive for HCV-Ab using enzyme linked immunoassorbant assay (ELISA) III and negative for hepatitis B surface antigen (HbsAg) and antinuclear antibodies (ANA). Patient's viral load was measured using branched deoxyribonucleic acid (DNA) signal amplification test (chiron b DNA 2.0 assay - quantiplex). There was no contra-indication for the use of interferon and ribavirin. All patients included had never received alpha-interferon or ribavirin before, alone or in combination. Patients in the child-bearing period, agreed to use the contraceptive methods to avoid pregnancy during and 6 months after treatment. The protocol design was explained to the patient treated, as well as the possibility of increase liver enzymes with treatment and the side effects of the drugs used. Patients with normal liver enzymes fulfilling the inclusive criteria were included as group A and patients with abnormal liver enzymes as group B. Viral load, HCV genotype and liver biopsy were carried out before entry. Patients in both groups were given one month treatment with alpha-interferon 2b (Intron A 3 million units, Shering-Plough) subcutaneously together with ribavirin 800 mg in 2 divided doses daily for one month (induction), followed by alpha-interferon 2b, 3 times a week with daily ribavirin for 11 months (same dose). Patients were followed monthly and viral load level was repeated at 12 months (end of treatment) and 6 months off treatment. Those tested negative by quantiplex (<0.2 meq/ml) were confirmed using qualitative PCR assay (Roche Amplicor monitor test).

Definition of response. End of treatment response (ETR): persistently normal liver enzymes together with quantitative viral load <0.2 meq/ml and negative qualitative test at end of treatment. Sustained virologic response (SVR): persistently normal liver enzymes 6 months after stopping treatment together with quantitative viral load <0.2 meq/ml and negative qualitative test.

Statistics. For continuous variables t-tests were used if comparing 2 groups. Chi-square was carried out to analyze group difference for categorical variables. All tests were 2 tailed and a P-value of <0.05 was considered significant.

Results. Out of 12 patients included in group A, only 10 patients agreed to be treated. Out of 10 patients, there were 4 males (40%) and 6 females

(60%). Age range between 25-58 years (mean 47.3 years). All were asymptomatic. Liver biopsies showed variable degrees of chronic inflammatory changes with no cirrhosis. Viral load ranged between 0.26-11.84 meq/ml (mean 2.73 meq/ml). Two patients had genotype 1b, one patient had genotype 1a + 1b, 2 patients had genotype 3 and 5 patients had genotype 4, **Table 1**. Patients response in group A were compared to patients with abnormal liver enzymes in Group B (control group), who were followed during the same period. There were 34 patients included initially in group B, however only 30 patients completed the study as per scheduled protocol; (3 patients lost to follow-up during treatment and one patient developed severe fatigue with malar maculopapular rash). Age of patients in group B ranged from 28-57 years (mean 43.1 years), 18 patients were male (60%) and 12 patients were female (40%), 5 patients were complaining of fatigue and 2 patients of itching. Five patients had established liver cirrhosis and 25 patients had variable degrees of chronic inflammation with no cirrhosis. Viral load ranged from 0.22 - 55.8 meq/ml (mean 8.56 meq/ml). Five patients had genotype 1a, 5 patients had genotype 1b, 2 patients had combination of 1a + 1b, one patient had genotype 2, one patient had genotype 3, 15 patients had genotype 4 and one patient had genotype 1a + 4. Twenty percent of patients in group A (2 patients) had genotype 2 or 3 as compared to 6.7% of patients in group B (2 patients). Eighty percent of patients in group A (8 patients) had genotype 1 or 4 as compared to 93.3% (28 patients) in group B. Genotype distribution was not statistically significant

Table 1 - Patients' characteristics and response in group A.

Patient N	Sex	Age	Quantiplex (meq/ml)	Genotype	ETR	SVR
1	M	42	9.38	1 b	Yes	No
2	F	58	11.84	4	Yes	No
3	M	37	1.04	4	No	No
4	F	48	0.64	4	Yes	No
5	F	49	0.78	1 b	Yes	Yes
6	M	37	0.45	4	Yes	Yes
7	M	43	1.36	4	Yes	No
8	F	25	0.26	3	Yes	Yes
9	F	50	0.89	1a + 1b	Yes	No
10	F	35	0.71	3	Yes	Yes

N - number, ETR - end of treatment response, SVR - sustained virologic response, M - male, F - Female

Table 2 - Response rates in group A and B.

Group	ETR %	SVR %
A	90	40.0
B	60	43.3
P-value	0.124	0.731
ETR - end of treatment response, SVR - sustained virologic response		

different between both groups ($P=0.254$). Forty percent of patients in group A (4 patients) were younger than 40 years as compared to 46.7% (14 patients) in group B. Sixty percent of patients in group A (6 patients) had low viral load (<1 meq/ml) as compared to 23.3% (7 patients) in group B ($P=0.052$). Only one patient (patient 3) developed increase liver enzymes, during the 5th month of treatment and persisted after end of treatment, however, a repeat genotype testing at the 9th month of treatment showed co-infection with genotype 1a + 4 instead of genotype 4 which were reported initially. In addition, another patient (patient 7) developed increased liver enzymes that was discovered 3 months after stopping treatment. End of treatment response in group A was 90% (9 patients) as compared to 60% (18 patients) in group B ($P=0.124$). Sustained virologic response in group A was 40% (4 patients) as compared to 43.3% (13 patients) in group B ($P=0.731$), **Table 2**. None of the patients in group B who had SVR had liver cirrhosis.

Discussion. The long-term outcome of untreated patients chronically infected with HCV and normal liver enzymes are still unknown. One study confirmed that liver fibrosis progression in this group is very slow.⁵ Mostly, the studies have shown that most of these patients' liver biopsy showed mild liver inflammation.^{6,7} Studies treating patients with hepatitis C focused on those patients with abnormal liver enzymes with only a few pilot studies using alpha-interferon therapy in patients with chronic hepatitis C and normal liver enzymes. In this study, the number of patients included during the study period was small as compared to patients with abnormal liver enzymes which may reflect the prevalence of this group of patients in our country (26.1%). This percentage, (12 patients out of 46 patients) will be less when corrected using all patients with chronic liver disease secondary to HCV including decompensated and the end stage disease followed during the same period who were not included in the study. The response rate with induction combination therapy in patients with normal liver enzymes was similar to patients with increase aminotransferase levels. This result is

different from that reported in previous studies with SVR of 13%.⁸⁻¹⁷ This is probably due to the combination therapy used in this study as compared to other studies where interferon monotherapy was used. Also, patients were treated for 12 months as compared to other studies (6 - 12 months). In addition, induction dosing of interferon was used initially in the first month which, probably has played a role on increased response by earlier decrease of viral load and hence less chance of viral mutation and development of quasispecies. Another concern regarding treating patients with normal aminotransferase levels is the possibility of increased enzymes during or after therapy at a rate of 48% due to interferon immunomodulatory activity.⁹⁻¹⁵ However, only 20% developed an increase in liver enzymes, which could be due to coinfection with another genotype during treatment in one patient. Patient's viral serologic was not very different between groups A and B. Genotype distribution was relatively similar among both groups.^{3,6,17} A higher proportion of patients in group A had lower mean viral load which was not found in other studies.^{3,18,19} The results of liver histology in group A showed less severe inflammation compared to group B which is consistent with other studies.^{3,6,7,11-13,17,19}

In conclusion, the study showed a similar response rate to induction combination therapy in patients with normal and abnormal liver enzymes who are chronically infected with hepatitis C. Currently, there is no rationale to treat patients with normal liver enzymes infected with HCV. More controlled trials are needed in the future to confirm the benefit and cost effectiveness of treating this group of patients.

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