Role of interferon anti body in predicting the response to interferon therapy in HCV patients

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Abstract

Objective: To see the frequency of formation of interferon antibodies in patients receiving alpha interferon and evaluate their role in treatment response.

Methods: Patients with chronic Hepatitis C receiving alpha interferon three times a week along with daily ribavarin in two gastroeneterolgy departments of public hospitals, running hepatology clinics were studied. Blood for interferon antibodies in most (71) cases was collected around 5th month of therapy, sera were stored and analyzed in batches. Sera of 134 patients was analyzed, of whom 44 were taking Interferon 2a and 90 were taking 2b.

Results: Of 134 cases, 17 showed the presence of antibodies in titers of over 50 units and 5 of these showed no response to interferon treatment (6%). Majority (78) of the cases had antibody levels of less than 20 followed by 39 cases whose levels ranged between 20-50 units.

Conclusions: Interferon antibodies are formed in a small percentage of cases receiving interferon and that too are in such low titers that they are not hampering the treatment. Serial antibody levels may be done to see if they remain stationary or increase with the continuation of the therapy (JPMA 57:581;2007).

Introduction

Hepatitis C is one of the commonest liver diseases seen world over and is a major cause of liver transplantation in USA.[1] In Pakistan the frequency of this infection in the general population is around 4-7%[2] but is a major cause of chronic liver disease and its sequlae. Interferon with ribavarin is the recommended treatment for viral eradication with cure rates varying between 70-90% in those carrying genotype 3, other types have low cure rates.[3]

Numerous studies have shown that antibodies also called auto antibodies or natural antibodies which react with a variety of self antigens are found in normal persons as well as patients suffering from inflammatory or infectious diseases.[4,5] This rare phenomenon of auto antibody production is strongly enhanced when self antigens are used in high doses as treatment drugs. Examples of such antibodies are antibodies to factor VIII, anti insulin antibodies, antibodies to erythropoietin and GM-CSF and interferon. It is important to note that antibodies inhibit the function of the particular cytokine and their production is undesirable when self antigen is administered as therapy.[6]

Interferon (IFN) antibodies are produced during treatment for viral or neoplastic diseases. Natural antibodies to IFN have been found in the serum of normal individuals[7-9] and patients with autoimmune diseases[10,11] viral infections[12] or tumours[13] but development of antibodies is pronounced in those receiving exogenous

interferon. Both neutralizing and non neutralizing (binding) antibodies have been detected but neutralizing antibodies are associated with failure of IFN therapy. Binding antibodies prevent normal clearance and degradation of administered IFN alpha.[14] Though these antibodies appear in both responders and non responders but they appear much earlier in non responders than in responders.[15,16] IFN beta is produced from Chinese hamster ovary cells or E coli cultures. The biological and biochemical characteristics of interferon's especially their relative antigenicites are different and therefore cannot be compared with each other.

Factors that play some role in the production of antibodies to IFN alpha are race, disease type, route of administration, schedule of dose, and type of IFN.

IFN antibodies are found more frequently in patients receiving IFN for tumours than in those receiving it for infectious diseases[17] and most literature describes production of auto antibodies in small and insignificant amount in these cases. Patients with HCV who have no neutralizing antibodies and who show a flare in ALT usually develop binding antibodies and thus antibody production can influence the outcome of therapy.[18-20] The present study was done to see the antibody production in those receiving either interferon alpha 2a or 2b for chronic hepatitis C.

Patients and Methods

Patients with chronic HCV related liver disease attending the liver clinic of PMRC research centre Jinnah Postgraduate Medical Center, Karachi and Khyber Medical College, Peshawar who were receiving interferon were selected for the study. All patients were HCV positive, PCR positive, had more than twice raised ALT for over 6 months and had compensated liver disease as seen on ultrasonography, serum albumin and endoscopy. All patients were taking either alpha 2a or 2b interferon at a dose of 3 MIU three times a week along with ribavarin 800-1200 mg daily.

Two milliliter of blood was taken from each patient, serum separated and stored at minus 5 degrees for analysis. The procedure of antibody testing was done according to the steps given in the catalogue.[21]

The response during therapy was assessed by monthly monitoring of ALT (normalized within 8 weeks). Those completing 6 months of therapy had a PCR done prior to stopping IFN. Response was defined as complete normalization of ALT for 4 months or more after starting IFN along with an undetected PCR at 6 months of therapy. Non response was defined as a positive PCR at 6 months with or without a raised ALT.

Results

A total of 134 sera were collected from 134 patients receiving interferon for HCV infection. All patients were over 19 years of age. Of the total, 44 patients were taking interferon 2a and 90 interferon 2b. The gender and duration of IFN therapy at which the sera were collected is shown in Table. Majority (71) of the samples were taken at 6 months of interferon therapy.

Table. Gender and duration of IFN therapy (n=134).

	2a			2b		
Months	**Male**	**Female**	**Total**	**Male**	**Female**	**Total**
1st	6	5	11	8	3	11
2nd	1	3	4	3	1	4
3rd	3	1	4	11	5	16
4th	3	1	4	1	2	3
5th	3	1	4	1	1	2
6th	14	3	17	41	13	54
Interferon antibody values						
< 20	20	10	30	28	19	47
20 - 50	9	2	11	24	4	28
> 50	1	2	3	13	2	15
Total	**30**	**14**	**44**	**65**	**25**	**90**

Interferon antibody values in both 2a and 2b recipients are shown in Table. According to the leaflet enclosed with the kit, antibody levels of over 40 should be taken as technical cut off values, while in our study we took 50 as the cut off (21). Majority of the cases (78) had antibody levels of less than 20 followed by 39 cases having values ranging between 20-50. Only 17 cases had values over 50, response to IFN in these 17 cases was evaluated and 11 were found to be responders (PCR negative at 12 weeks), 5 were non responders (PCR positive) and 1 was lost to follow-up.

Discussion

Of 134 sera checked for interferon antibodies only 17 were found to have titers of over 50 units and of these only five showed non response (6%). Globally end of the treatment response varies between 70-80%[22] but sustained response is around 50-60%.[23] The variation in response is dependant on the serotype, response being good in type 2 and 3 but poor in type 1.[22] Treatment duration is 24 weeks for type 2 and 3 and 48 weeks for all other types. In Pakistan majority of the cases have serotype 3[24] which has the best response to 24 weeks therapy with interferon.

Interferon antibodies are more frequently formed in those receiving beta interferon Vs those getting alpha, but even in those receiving alpha interferon it is generally those

who are either taking a high dose of interferon or are taking the drug for a long time like in mycelia or multiple sclerosis. In liver disease usually alpha interferon is given and also in a low dose and in most cases therapy does not extend beyond 12 months. In Pakistan a six month therapy of 3 million units three times a week is recommended, which is a low dose and short course, while the highest dose of alpha interferon is pegalated interferon 180micograms every week for 6-12 months and even with this dose antibodies have been infrequently reported.

The present study shows that antibody production with alpha interferon in patients receiving treatment for chronic HCV infection is low and is not hampering with the treatment response. In this study single blood sample was taken from each patient any time after 3 months of initiation of the therapy, therefore it is possible that some cases might have been under reported as that might have produced low level antibodies at that time. It would be worthwhile to collect serial samples in few cases and see if values go up each month or are stable irrespective of the duration of therapy.

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