The Effects of Interferon and Ribavirin in Chronic Hepatite C

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The chronic hepatitis C is a frequently problem in worldwide, the number of infected individuals is high and go on, getting a public health problem [1]. In Romania there are nearly 1 million persons infected with hepatitis C virus, the scope of spreading is related with specific risk factors. An important number of infection with hepatitis C virus present simultaneous extrahepatic manifestations proved to be alone manifestation tracing; its important for diagnosis and treatment. We analyzed the effects of interferon and ribavirin in chronic hepatitis C in General C.F. Hospital Sibiu, between 2008 – 2012. The association between infection with hepatitis C virus and extrahepatic manifestations is important to be recognized for adequate diagnosis tests. By comparing the results of therapy in patients with hepatic and extrahepatic manifestations, the study found that 30 patients (58.83 %) with liver manifestations had an incomplete response versus 10 patients (26.32 %) with extrahepatic manifestations; 11 patients (21.54 %) with hepatic manifestations had a complete response versus 3 patients (7.89 %) with extrahepatic manifestations; and 10 patients (19.63 %) with hepatic manifestations did not respond to treatment versus 25 patients (65.79 %) with extrahepatic manifestations. Analyzing the results of antiviral therapy in patients with hepatic manifestations and those with extrahepatic manifestations, antiviral treatment appears to be more advantageous in cases with only hepatic manifestations.

Keywords: chronic hepatitis, hepatitis C virus, extrahepatic manifestations, interferon, ribavirin, treatment

Without hepatic manifestations in chronic hepatitis C appears other extrahepatic manifestations [1] such as cryoglobulinemia mixed is the most frequently (associated sometimes with membranoproliferative glomerulo-nephritis), other manifestations are endocrine manifestations (diabetes mellitus, hypothyroidism), haematological manifestations – aplastic anemia, thrombocyto-penia purpura, lymphomas [2-6].

In accordance with recent studies lichen planus, chronic urticaria, corneal ulceration, uveitis and lung fibrosis represents other extrahepatic manifestations. These manifestations are rarity [2,7].

Experimental part

The study is retrospective based on 162 cases of chronic hepatitis with antibodies HCV positive hospitalized in Departments Medical of General C. F. Hospital Sibiu between 2008 – 2012. 78 cases with chronic hepatitis C were followed up prospective for duration of hospitalization. Each patient had a clinical observation paper with personal dates, personal pathological and heredity history, the anamnesis and clinical dates, the results of lab tests and paraclinical investigations. The study protocol was approved by the Ethics Committee of General C. F. Hospital Sibiu.

It was filled the debut of clinical manifestations, the moment of diagnosis, the way of trace out the infection with hepatitis C virus, epidemiological inquest for established the possible infection moment. All informations are based on personal assertions.

At each patient was made a short case presentation for evidence the particular aspects of diagnostic, evolution and treatment. Patients were included in the study after signing the informed consent form enrolment.

The including criteria are patients with hepatitis C infection confirmation by ELISA generation II or III, with hepatic and extrahepatic manifestations.

The exclusion criteria are patients with simultaneous infection with hepatitis B virus and HIV; patients with alcoholic hepatitis; patients with autoimmunity hepatitis or with autoimmunity manifestations; patients with liver cirrhosis and hepatocellular carcinoma, with hepatitis C virus infections confirmating by ELISA generation II or III.

The diagnosis of chronic hepatitis C virus was established by: anamnesis criteria (epidemiological inquest); clinical criteria; laboratory criteria (hepatic functional test and etiological confirmation); hystopathological criteria.

The test which was used for evidence the antibodies HCV was ELISA generation II or III (Murex anti-HCV-versions III, Menolisa (R) anti-HCV PLUS, ORTHO (R) HCV 3.0 ELISA).

Data collected were pooled, processed and analyzed biostatistics, using test X (2) (to calculate the index p) and for risk assessment and the assessment of the association between different parameters was performed using the statistical analysis program EPIINFO 2000.

Results and discussions

The group of 162 cases with chronic hepatitis with antibodies HCV positive are composed by 102 females (63%) and 60 males (37%). In our study we observed that it was a preponderant affection of age 60 – 69 years (27.16%), followed up by age 50 – 59 years (25.92%). The average age was 54.46±13.15 years. In our group, 132 patients proceed from urban environment (81%) and 30 patients from rural environment (19%). 53 patients (33%) present without hepatic manifestation, extrahepatic manifestations, and 109 patients present only hepatic manifestations. The distribution of cases with extrahepatic

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manifestations is: 16 patients with endocrine manifestations (30.18%). One third of patients present extrahepatic manifestations which showed high frequency of extrahepatic manifestations [8-14].

Regarding the etiopathogenic treatment, from the group of 162 cases of chronic viral C hepatitis, 89 patients (54.93%) received antiviral treatment according to the recommended regimes (table 1). The treatment regimens used were standard antiviral-associated immunosuppressants in cases with extrahepatic manifestations such as mixed cryoglobulinemia, thyroiditis or chemotherapy in cases with leukemia and lymphoma.

The antiviral treatment regimes used were different depending on the time period in which these patients were treated, according to the recommendations and approvals of the National Health Insurance House. The treatment regimens used were:

- only interferon for 6 months;
- interferon and ribavirin for 6 months;
- interferon and ribavirin for 12 months;
- pegylated interferon and ribavirin for 6 to 12 months.

Immunosuppressive treatment consisted of corticotherapy in variable doses associated with or without Azathioprine or Cyclophosphamide. Corticotherapy has been shown to occur in some forms of hepatitis associated with cryoglobulinemia, manifested by cutaneous vasculitis or glomerulonephritis, especially in severe forms with much increased cryocytosis. Corticotherapy has also been used in cases of thyroiditis and lichen planes. Plasmapheresis was used as a therapeutic only in a patient with chronic viral C hepatitis C with mixed cryoglobulinemia. Of those who completed etiopathogenic therapy, 40 patients (44.94%) had an incomplete response, 14 patients (15.74%) had a complete response and 35 patients (39.32%) had no response.

By comparing the results of therapy in patients with hepatic and extrahepatic manifestations, the study found that 30 patients (58.83%) with liver manifestations had an incomplete response versus 10 patients (26.32%) with extrahepatic manifestations; 11 patients (21.54%) with hepatic manifestations had a complete response versus 3 patients (7.89%) with extrahepatic manifestations; and 10 patients (19.63%) with hepatic manifestations did not respond to treatment versus 25 patients (65.79%) with extrahepatic manifestations (table 2).

Analyzing the results of antiviral therapy in patients with hepatic manifestations and those with extrahepatic manifestations, antiviral treatment appears to be more advantageous in cases with only hepatic manifestations. Incomplete response occurs in cases with hepatic manifestations of 30 patients (58.83%) versus 10 patients (26.32%) with extrahepatic manifestations without statistical significance (p value = 0.34, Odds ratio = 1.46, 63 <OR <3.46 and Relative risk = 1.11; 0.9 <RR <1.37). The complete response occurs in cases with hepatic manifestations - 11 patients (21.54%), unlike cases with extrahepatic manifestations 3 patients (7.89%), also without statistical significance (p value = 0.38 ; Odds ratio = 1.78; 0.43 <OR <8.44 and Relative risk = 1.17; 0.87 <RR <1.57). Lack of response occurs predominantly in patients with extrahepatic manifestations (65.79%) versus 19.63% in those with hepatic manifestations with statistical significance (p value = 0.00002, Odds ratio = 0.19, 0.08 < OR <0.46 and Relative risk = 0.42; 0.25 <RR <0.72, fig. 1).

In cases of mixed cryoglobulinemia which, in addition to antiviral treatment, also underwent immunosuppressive treatment, its effect on the clinical manifestations of cryoglobulinemia was monitored both at the end of

Etiopathogenic treatment	*Number of cases*	*Percent*
With treatment	**89**	**54.93 %**
No treatment	**73**	**45.07 %**

Table 1
THE DISTRIBUTION ACCORDING TO ETIOPATHOGENIC TREATMENT

Response type	*Hepatic manifestations*	*Extrahepatic manifestations*
Incomplete	30 (58.83%)	10 (26.32%)
Complete	11 (21.54%)	3 (7.89%)
No answer	10 (19.63%)	25 (65.79%)

Table 2
THE DISTRIBUTION BASED ON RESPONSE TO ETIOPATHOGENIC THERAPY IN PATIENTS WITH HEPATIC AND EXTRAHEPATIC MANIFESTATIONS

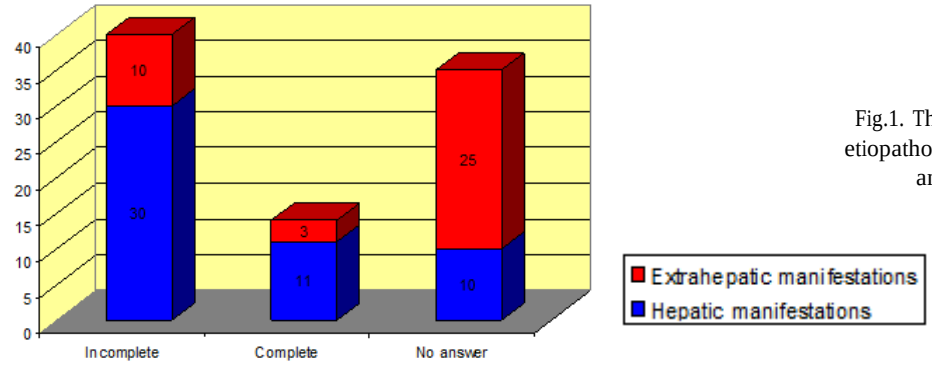

Fig.1. The distribution based on response to etiopathogenic therapy in patients with hepatic and extrahepatic manifestations

Table 3

DISTRIBUTION BASED ON IMPROVEMENT / DISAPPEARANCE OF CLINICAL MANIFESTATIONS OF CRYOGLOBULINEMIA SECONDARY TO PATIENTS WITH ANTIVIRAL THERAPY

Clinical Manifestation	*Amelioration / disappearance at the end of antiviral treatment*	*Amelioration / disappearance after 6 months with antiviral treatment*
Purpura (n=3)	1	–
Arthralgia (n=45)	35	23
Glomerulonephritis (n=3)	2	–

treatment and during 6 months after the end of the treatment and at the end of the follow-up period.

We analyzed the evolution of purpura and other clinical manifestations, cryoglobulinemic glomerulonephritis, arthralgia. The results were as follows: amelioration or disappearance of purpura in 1 case of the 3 cases, improvement of arthralgia in 35 of the 45 cases.

In relation to glomerulonephritis, improvements occurred in 2 patients, especially in terms of proteinuria level. In one patient, interferon treatment produced worsening of glomerulonephritis with rapid progression to renal failure. At 6 months after discontinuation of antiviral treatment, recurrences were common in both purpura and glomerulonephritis (table 3).

We have assessed the response to treatment (clinical improvement or disappearance of cutaneous lesions), immunological (disappearance of cryoglobulins) and virological treatment both at the end of treatment (6 or 12 months) and prolonged response 6 months after discontinuation of treatment and End of the tracking period. I have noticed that most of the patients who have recurred did so during the first 6 months, then until the end of the clinical follow-up period, the percentage of relapses was very low. The clinical response was in parallel with the immunological response, the values being comparable.

Our observation is that antiviral treatment can improve the clinical picture of vasculitis, even in the absence of prolonged virological response. The disappearance of cryoglobulins in patients with no virological response could be due to their marked quantitative reduction to undetectable levels by common means. In most cases, the recurrence of vasculitis was preceded by the recurrence of serum cryoglobulins.

Another observation was that patients who had a sustained virological response sustained clinical vascular remission (the clinical, immunological and virological long-term remission rates are Comparable). The relapsed patients tended to repeat relapses requiring the resumption of antiviral treatments, sometimes with more doses or in associations.

In two cases of mixed cryoglobulinemia manifested by purpura and glomerulonephritis, maintenance treatment with low doses of long-acting pegylated interferon was proposed, the results to be evaluated.

Determination of the HCV genotype is important, on the one hand, because it is a predictor of the response to treatment and, on the other hand, allows the determination of the duration of the antiviral treatment.

Patients infected with genotype 2 and 3 will be treated with pegylated interferon and ribavirin for 6 months, these patients being highly susceptible to sustained virological response (over 80%). Individuals infected with other genotypes require 1 year of treatment with low probability of sustained virological response (40-50%) [15, 16].

Ribavirin, an antiviral agent, is the best example of potent molecule possessing a triazole nucleus [17]. Tibavirin is active against a number of DNA and RNA viruses [18].

Determination of viral load is a component of virological evaluation of antiviral patients. Patients infected with genotype 1 and low viral load (below 800.000 IU / mL) are highly likely to have sustained virological response compared to patients with high viral load (over 800.000 IU / mL).

In addition, early viral kinetics during antiviral treatment is a predictor of the type of response. In patients infected with genotype 1 treated with pegylated interferon and ribavinin, the lack of a significant decrease in viral load at 12 weeks (less than 2 log10) has a predictive value of lack of response and, consequently, treatment is discontinued [15,16].

In patients where the 12-week viral load decreases by more than 2 log10, treatment continues for up to 24 weeks and then discontinued if HCV RNA remains positive. In patients infected with genotype 2 and 3, viral load determination is not required for virological assessment because most patients have a decrease of more than 2 log10 at 12 weeks of treatment. Thus, patients with genotype 1 and 4 have a high viral load with a low rate of sustained virologic response (with genotype 3 particularities) [15, 16, 19].

Conclusions

The extrahepatic manifestations were presented at one third of patients that means extrahepatic manifestations appear with a high frequency. The most frequent extrahepatic manifestations was: cryoglobulinemia mixed both symptomatic – 5 cases (9.43%) and asymptomatic – 17 cases (32.17 %), followed by diabetes mellitus without insulin – 11 cases (20.75 %). Analyzing the results of antiviral therapy in patients with hepatic manifestations and those with extrahepatic manifestations, antiviral treatment appears to be more advantageous in cases with only hepatic manifestations. Antiviral treatment may

improve cryoglobulinemia, but relapse after treatment is common; The alternative treatment in these patients is treatment with low-dose pegylated interferon. The sustained virological response is associated with the remission of vasculitis. Chronic hepatitis with HCV is commonly associated with extrahepatic manifestations, the most common being mixed cryoglobulinemia. If in some of the extrahepatic manifestations the relationship with HCV has been clearly established, in the other is only suggested. The number of extrahepatic manifestations in chronic hepatitis with HCV is steadily increasing and remains an open field of research.

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