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ANTIVIRAL THERAPY AND METABOLIC SYNDROME IN PATIENTS WITH CHRONIC HEPATITIS C

Manuela Arbune[1], P. Dăscălescu[2]

[1.] *"Dunărea de Jos" University Galați*
[2.] *Infectious Diseases Hospital Galați*

Abstract. Hepatitis C virus (HCV) infection affects 3% of the people all over the world. The heterogeneous viral genotypes correlate with prognosis of the disease. Genotype 1 is characterized by the low response to interferon and prevails in Romania. The relation between metabolic syndrome (MS) and the effectiveness of treatment with Peg Interferon and Ribavirin was assessed in 57 patients with chronic hepatitis C recorded in the Infectious Diseases Hospital Galați during 2007-2009. The retrospective study was based on analysis of medical records, therapeutic protocols and the criteria of metabolic syndrome. The virologic response was 92% at 24 weeks and it was sustained at 72 weeks in 56.16% of cases. MS was diagnosed in 31% of patients with HCV and it was significantly correlated with weak viral response at 24 weeks. The study concluded that failure of treatment with Peg Interferon and Ribavirin is related to MS in patients with chronic hepatitis C. Systematic assessment and improvement of metabolic syndrome before the antiviral treatment should optimize the virologic response of HCV.
Keywords: hepatitis C, metabolic syndrome, Peg Interferon, Ribavirin, virologic response

Background

Infection with HCV is one of the main topics of the present public health. An estimated 170 million people globally are living with HCV, but a rising prevalence is expected because of 3-4 million yearly new infections with predicted 80-90% chronic trend, if an efficacy vaccine lodge is unavailable (Grigorescu M, 2009). The characteristic of HCV is the genetic heterogeneity with 6 genotypes correlated with prognostic of infection. Associated Pegylated Interferon and Ribavirin was a hopefulness therapy of HCV during the past few years, but no response and relapsing infections are still frequent therapeutic results. The rate of treatment failure ranges between 43-50% for genotypes 1 and 4 and 10-15% for genotypes 2 and 3.

Assessment of HCV antiviral treatment proved that fast and early virologic responses are predictors of sustained virologic response to treatment (SVR).

Latest researches mention predictor factors for therapeutic failure and the need to develop new strategies for HCV management. HCV infection is a systemic disease with metabolic consequences. The disorders of glucose metabolism are negative predictors for the virologic response on therapy with PegInterferon and Ribavirin. Insulin resistance was reported in 69% of patients with HCV (Harrison SA, 2010). Recent trials evidence high risk of ischemic cardiac disease in patients with HCV, related to complex atherogenic mechanisms, including increase of inflammation and oxidative stress, endothelial dysfunction and direct viral injury. It is expected that future efficient management of HCV will improve the risk of cardiovascular diseases.

Materials and methods

The observational study on patients with confirmed chronic hepatitis C and antiviral treatment was retrospectively performed, based on medical

Manuela Arbune
Infectious Diseases Hospital "Sf. Cuvioasa Parascheva"
393 Traian Street, Galați, Romania
E-mail: arbunemanuela@yahoo.com

records of the Infectious Diseases Hospital Galați during 2007-2009. The criteria for initiation and monitoring of antiviral treatment followed the protocols regarding HCV, developed by the National Health Insurance House. The coinfections with HCV and HIV were excluded. Genotyping was not available. The research was approved by the Ethical Committee of the hospital. We collected demographic, behavioural, epidemiological, clinical, biological and therapeutic data. Anthropometric parameters (weight, height, waist circumference) and arterial blood pressure by standard methods are systematically evaluated for all the patients in our clinic. Blood levels of glucose, cholesterol and triglycerides were usually measured. Before antiviral treatment of HCV, the diagnostic of metabolic syndrome was considered in the presence of 3 out of 5 criteria of the National Cholesterol Education Program (NCEP) Adult Treatment Panel III.

Statistical analysis was performed using „Statistical Analysis Toolpack Xlstat" software. The level of significance for statistical tests was considered $p<0.05$.

Results

57 patients were participants to the study. The characteristics of the patients are summarised in table I.

Only few clinical symptoms were found in the medical history of the studied group. Chronic fatigue syndrome and dyspeptic syndrome are variably recorded in medical documents. Extrahepatic manifestations occurred as expression of immunologic disorders in HCV infection and were dominated by dermatological appearances (21.5%) such as lichen planus (3/57), erythema nodosum (2/57), porphyria cutanea tarda (1/57) or other dermatitides (6/57). Acquired cryoglobulinemia was found in 7% (4/57) of patients and 8.7% (5/57) had positive rheumatoid factor. Co-infections with hepatitis B virus (HBV) were reported in 7% (4/57) of patients.

The comorbidities that prevailed were: metabolic disorders (44.5%), digestive diseases (12.2%) and extrahepatic tumours (5%) (figure 1).

According to NCEP definition for metabolic syndrome, 31% (22/57) of patients complied with 3/5 diagnostic criteria. The frequencies of characteristic criteria were 43.5% (25/57) low HDL-cholesterol, 35.08% (20/57) high triglycerides, 31.57% (18/57) central obesity, 26.31% (15/57) arterial hypertension, 10.5% (6/57) diabetes.

The events related to PegInterferon and Ribavirin were flulike syndrome (100%), depression (26.3%), arthralgia (17.5%), cough/interstitial pneumonia (14%), nephropathy (12.4%), hyperpigmentation (2%). Depression and hyperpigmentation exacerbated during the therapy. On the contrary, most of the flulike syndromes improved until the end of treatment. 92% of patients were haematologically normal at baseline, but they developed: 42% (24/57) anaemia, 45.6% (26/57) neutropenia and 38.5% (22/57) thrombocytopenia during the treatment.

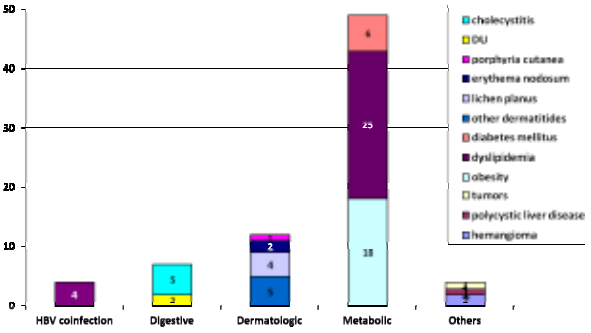
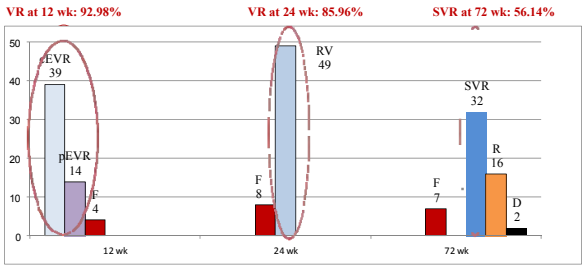


Figure 1. Co-morbidities in HCV infected patients on treatment notification date

At 12 weeks of treatment 7% (4/57) of patients were nonresponders and stopped the therapy. Early virologic response (EVR) was achieved in 93% (53/57) patients, but only 68.4% (39/57) among them had complete EVR (cEVR). Partial early virologic response (pEVR) was obtained in 24.56% (14/57) of patients and 11/14 (78.57%) of them were late responders with undetectable HCV-RNA at 24 weeks of treatment. Patients with complete viral suppression after 12 or 24 weeks continued the treatment until 48 weeks. Sustained virologic response (SVR) at 72 weeks was achieved in 56.14% of patients (figure 2).



cEVR - complete early virologic response: undetectable HCV-RNA at week 12 by quantitative PCR
pEVR - partial early virologic response: ≥2 log drop in HCV-RNA at week 12 by quantitative PCR
EVR- early virologic response: cEVR or pEVR
LVR – late virologic response: ≥2 log drop in HCV-RNA at week 12 and undetectable HCV-RNA at week 24 by quantitative PCR
SVR – sustained virologic response: **EVR** and undetectable HCV-RNA at week 72 by quantitative PCR
NR – Nonresponder: <2 log drop in HCV-RNA at week 12 or detectable HCV-RNA at week 24
R – Relapse: EVR and detectable HCV-RNA at week 72
F – Failure: NR or R
D – deaths

Figure 2. Virologic response (VR) of HCV at 12, 24 and 72 weeks of treatment

N=57		
Demographic data	Median age (range)	49 [29; 64]
	Sex ratio (F/M)	1.45 (45/31)
	Living area (U/R)	1.17 (41/35)
Behavioral data	Smokers	11 (19.2%)
	Alcohol consumer	4 (7%)
	Heterosexual stable	57 (100%)
Epidemiologic risk factors for HCV infection	Surgical/invasive procedures	16 (28%)
	Transfusion	15 (26.3%)
	Unknown	26 (45.6%)
	Dentistry procedures	57 (100%)
Biologic data	Mean hemoglobin (range)	13.8 [9.6; 16.9] g/dl
	Mean leukocyte no. (range)	6618 /mm^3 [2600; 14900]
	Mean thrombocyte no. (range)	224087/mm^3 [103000; 358000]
	Mean ALAT (range)	124.33 UI [22; 349]
	Mean blood glucose (range)	94.33 mg/dl [67; 142]
	Mean trigl. (range)	115.3 mg/dl [34.5; 401]
Virologic data	Mean HCV-RNA (range)	1246858 c/ml [38888; 6134761]
Histologic data - Metavir score*	Inflammation A1/2/3	6/ 44/ 3
	Fibrosis F 1/2/3/4	1/ 9/ 41/ 2

*4 patients with contraindication for liver biopsy

Table I. Overview of the characteristics of patients with HCV on notification date of antiviral treatment

Univariate statistic analysis of SVR at 72 weeks and EVR means the correlation between cEVR and the expectancy of SVR: p<0.001; OR=15; CI 95% [3.31; 67.80].

Treatment failure was recorded in 43.85% of patients, including nonresponders and relapsers at 72 weeks. Nonresponders after 24 weeks associated the MS diagnostic: p<0.001; OR = 13.2 CI 95% [2.97; 58.57]. Stratification of criteria for MS and statistical analysis of virologic response at 24 weeks point out the only significant influence of hypertriglyceridemia (p<0.001; χ^2 = 13.65; DF4).

Discussions

The main limit of the study is the small number of cases for statistical analysis. The retrospective design of the study enclosed heterogeneous groups. By example, thyroid evaluation was necessary since 2008 and the support of associated therapy was available for Erythropoetinum since 2008 and for Filgrastim since 2009.

Age analysis revealed 84% of patients over the age of 40, probably related to old nosocomial infections similar to the Romanian HIV epidemic and the low prevalence of intravenous drugs users in our region. No influence of age on virologic response was found at 12, 24 or 72 weeks, as opposed to other reports of lower virologic response over the age of 40 (Highleyman L., 2008). However, older age supposes higher risk for metabolic disorders and correlation of MS and nonresponders at 24 weeks was calculated. Unexpectedly, a 31% prevalence of metabolic syndrome in the HCV infected group was lower than the 42.8% prevalence in the general population (Matei C., 2008). Although insulin resistance should be very useful for metabolic assessment of HCV infection, these data were not available for this retrospective study. Regarding diabetes, the 10.3% (6/57) prevalence in the study group was higher than the 4.2% general prevalence in Romania, estimated by the Eurodiab study. In the study group, females and urban area living patients prevailed, but no statistical correlation with the virologic response was found.

Pinchoto A & al (2009) observed that an ALAT/ASAT ratio >1 is related to inflammatory histological findings, while values <1 point to advanced fibrosis. In our study group, 84.2% of patients displayed an ALAT/ASAT ratio over 1, but it is not correlated with histological inflammation or fibrosis,

probably because of different viral genotypes, ethnic peculiarities and accessory evolutive factors. The histological analysis considered Metavir scores with 88.6% severe necrosis and 92.8% middle or severe fibrosis. While 47% of patients recorded over 800000 c/ml HCV-RNA, there are no histological correlations with Metavir scores and virologic response.

Viral genotyping was not available, but we assumed an HCV genotype 1, prevalent in Romania. Related to other HCV genotypes, the therapeutic response of genotype 1 is consensually weaker, but variable rates of SVR are related to ethnicity and race. Comparative trials from USA regarding treatment of HCV genotype 1 reported 50% SVR in white non-Hispanic population, 34% in Latino population and 28% in Afro-Americans (Iuliano AD, 2009). SVR was 56.14%, much closer to that of white non-Hispanic population. The prognostic value of cEVR at 12 weeks for SVR at 72 weeks is in accordance with the researches of Mangia A (2008) and Martinot-Peignoux M (2010).

Present directions in HCV treatment should be focused on the management of difficult to treat patients, the differentiation of treatment length according to genotype, fast virologic response at 4 weeks, race and comorbidities, and last but not least, improving quality of life and therapeutic adherence.

Conclusions

The dominant profile of the patient with HCV treated with PegInterferon and Ribavirin was: female, over the age of 40, from urban area.

Frequent dermatologic, metabolic and immunologic comorbidities are revealed in HCV patients eligible on antiviral treatment.

Therapy of HCV was difficult to tolerate mainly because of haematological and depressive events.

Sustained virologic response at 72 weeks was 56.14%.

Complete early virologic response at 12 weeks is a predictor for sustained virologic response at 72 weeks.

The prevalence of metabolic syndrome is 31% and it predicts the risk of virologic failure at 24 weeks, especially in hypertriglyceridemic patients.

Systematic assessment and improvement of metabolic syndrome in eligible patients for HCV treatment should optimize the virologic response.

Abbreviations:

HCV: hepatitis C virus
EVR: early virologic response
SVR: sustained virologic response
MS: metabolic syndrome
HT: arterial hypertension

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