THE ANTIVIRAL THERAPY EFFECT IN PATIENTS WITH CHRONIC HEPATITIS C AND RHEUMATOID SYNDROME

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CHRONIC HEPATITIS C

The hepatic virus C (HCV) infection is still an important public health problem with significant impact and a growing frequency in many global areas.

Apart from the severe influence upon individual lifestyle, the hepatic C virus implies a permanent risk of pathogenic evolution and reaching the stage of complications. Among these, the most feared are viral hepatic C chyrrosis and hepatocellular carcinoma, with negative outcome and high rate of mortality.

It is nowadays admitted that hepatic C virus affects approximately 3% of the global population, with chronic infection concerning 170 million individuals. The transmission pathways includ:

- percutaneous pathway (by blood and blood products)
- non percutaneous pathway – sexual and perinatal transmission
- community transmitted hepatitis – with no defined etiology, most commonly by shared personal objects [1, 2]

The hepatic C virus has a 50 nm diameter and belongs to the Flaviviridae family and the Hepacivirus RNA monocatenary cathegory. The pathogenic mechanisms are: viral direct effect, steatosis, oxidative stress, genotype 3 and iron overload [1].

The clinical signs of chronic hepatitis C (CHC) such as cutaneous modifications, hepatomegalia, splenomegalia, extrahepatic manifestations, as well as the investigations (liver function, immunology, morphological and imagistical exploration) that are typical for chronic liver disease lead to the suspicion of chronic hepatitis C. Further on, this must be confirmed by the detection of anti-HCV antibodies and also by the identification of RNA-HCV viral load [3].

RHEUMATOID SYNDROME

Viral infections frequently imply joint disease, such as the rheumatoid syndrome. Thus, there is a constant need to understand how the arthritis is caused by the viral impact
and also, the immune reactions and the host particularities that influence the chronic inflammatory process [4].

The principal mechanism for the rheumatic manifestations is represented by the autoimmune disorders, as a result of the multiple genetic trigger factors (genetic background, HLA-DR4), and also environmental and immunological conditions that contribute to a disorganized reaction of the immune system.

Regarding the increased incidence of rheumatoid syndrome as part of the virus C liver infection, the similarities with the rheumatoid arthritis emerge. The inflammatory pathology, the eventual positive rheumatoid factor, the similar symptoms and the principals of treatment are such examples.

A thorough differential diagnose is thus needed, based on the distinction criteria of rheumatoid arthritis and the observation of different particularities of the two diseases, such as the anti citrullinated peptide (anti-CCP) antibodies which represent an early diagnose element for the rheumatoid arthritis.

TREATMENT OF CHRONIC HEPATITIS C

The CHC therapy main goals are the following:
- reducing mortality by blocking the HCV evolution towards complications – hepatocellular carcinoma
- improving the quality of life
- obtaining sustained viral response which is defined as plasmatic absence of HCV viral load 6 months after the end of antiviral therapy. This is also highly important in medical practice as an indicator of the therapy success, taking into consideration that sustained viral response is associated to an improvement of mortality and morbidity [2, 5].

The combination between pegilated interferon and ribavirine represents a basic element regarding CHC therapy. A 48 week treatment is necessary for genotype 1 patients and a 24 week treatment is recommended to genotype 2 or 3 patients. The aim of obtaining sustained viral response is based on decreasing viral load for more than 2log10 after 12 weeks of treatment.
The most important side effects of interferon are anemia, neutropenia and thrombocytopenia by myelosuppresion and also alopecia and flew-like symptoms. Ribavirine side effects include lymphopenia, rash, cough, hiperuricemia but the main one is hemolytic anemia [1, 3].

A very important aspect is represented by the therapy for the growing number of non-responding patients, many of whom have advanced liver damage. A treatment alternative that has been recently considered is combining the new triple therapy with PEG-IFN and ribavirine [3].

**TREATMENT OF RHEUMATOID SYNDROME**

The current treatment for rheuamtoid arthritis includes:
- early onset of therapy for preventing bone distruction
- updating treatment through different drug combinations for optimizing the results and blocking the disease [6]

The hepatitis C related rheumatoid syndrome often includes many of these principles of treatment. Nevertheless, the symptoms do not often request an agressive therapy and on the other hand, certain drug combinations are avoided due to the negative potential effect upon the liver disease.

The classical strategy for the treatement of rheumatoid arthritis is the use of analgesic drugs and also nonsteroid antiinflammatory substances (NSAID) that have proven their efficency in controlling the symptoms and the inflammation process through their capacity of inhibiting ciclooxygenase and proinflammation citokines.

The second line of treatment includes the use of oral or intra-joint glucorticoids. Their role is to diminish symptoms and to delay the erosive joint process.

Other solutions in case of persistance, progression and severeness of the rheumatoid syndrome and also when other treatment measures fail, are immunosuppressive agents and citokine targeted drugs that reduce the inflammation process and the joint disease evolution [6].
**SPECIAL PART**

**AIM OF STUDY**

- the evaluation of the symptoms and investigation results in two groups of patients diagnosed with chronic hepatitis C and rheumatoid syndrome in the presence/absence of antiviral therapy
- identifying the role of the antiinflammatory properties of interferon in decreasing chronic hepatitis C related joint disease
- a descriptive analysis of the patients with chronic hepatitis C and rheumatoid syndrome included in the study
- suggesting a drug combination that aims to avoid an aggressive or superficial therapy and to offer optimal results both for the regression of liver disease and also the control of the rheumatoid syndrome
- estimation of treatment adherence as a very important factor for an efficient treatment, by identifying the side effects and their incidence in studied patients, which may become a potential cause for therapy interruption

**PATIENTS INCLUDED IN THE STUDY**

This study has analysed a total of 50 patients diagnosed with chronic hepatitis C and rheumatoid syndrome. A group of 25 patients was submitted to a 12 month treatment with Peg-IFNa2a/ribavirine, associated to a small dose of NSAID.

**Inclusion criteria:**

- liver disease criteria: detectable viral load, elevated live cytolysis enzymes, age $\leq 65$, impulsional elastography fibrosis score $F \geq 1$
- rheumatic disease criteria: negative anti-CCP antibodies, mild elevation of inflammation markers, arthralgia in maximum 3 peripheric joints, morning stiffness of less than 30 minutes, absence of rheumatoid arthritis radiological modification
Exclusion criteria:

- confirmed rheumatoid arthritis by ACR diagnose criteria
- patients who refused the antiviral therapy
- patients without a complete anamnesis or evaluation
- the presence of crioglobulinemia and other inflammatory disease (ex: ginecological, otolaringological, dental) that could modify the inflammation markers
- other associated disease (liver, cardiac, pulmonary, neurological etc.)

METHOD OF THE STUDY

The study was structured in 4 phases:
1) Identification of eligible patients and their inclusion in the study
2) Therapy initiation
   - all patients received intermittent minimal dose of NSAID, when needed, for maximum 5 days/month
   - patients belonging to the first group initiated the treatment with Peg-IFNα2a -180 micrograms/week and ribavirine (800-1200mg/day)
3) Monitorizing the patients using an evaluation form that contains:
   - liver and joint symptoms at every check-up
   - levels of liver cytolysis and ultrasound investigation at the beginning of the study, then 3, 6, 12 months later
   - viral activity by dosing the plasmatic viral load
   - investigation of the inflammatory syndrome by dosing CRP and ESR at the beginning of the study, then 3, 12 months later
   - blood count every month and other serological investigations
   - side effects according to therapy
4) Statistical analysis of the data and comparing it to medical literature studies
RESULTS AND DISCUSSION

The description of the group of patients indicates a higher incidence of women (78%) and suits the general information on the topic, which shows that the rheumatoid syndrome affects the female gender more frequently [6]. On the other hand, men tend to develop chronic viral infection more often than women [1].

The great majority of patients came from rural areas (72%), a possible explanation for this being the more difficult access of these patients to medical services and also the constant exposure to risk factors that can influence the liver disease evolution and the extrahepatic manifestation onset.

The 5th decade of life was predominant (48%), matching the most common groups of age that are affected by the rheumatoid arthritis. Nevertheless, studies indicate that chronic hepatitis C is more frequent in the 6th decade of life [1, 6].

The risk factors that were most frequent are the following: dental interventions (72%), surgery interventions (44%), blood transfusions (30%) and high professional risk (24%). The results regarding these last pathways of transmission are similar to the epidemiological data of our country [1].

Regarding body mass index (BMI), normal weight was observed at 66% of patients, there were also obese patients (6%), overweight ones (24%) and also underweight patients (4%). Body mass index is important for the analysis of patients who are submitted to antiviral therapy taking into consideration that predictive factors for obtaining sustained viral response include a low BMI [2].

Liver disease was analysed using the new noninvasive methods in all patients undergoing antiviral therapy. The fibrosis level measured by Fibroscan was correlated with both elastography results and also the age of patients, with a statistical significant association between the fibrosis progress and the 6th decade of life (p<0,05). This result is also indicated by other studies that show the rapid evolution of fibrosis in elderly patients [7].

A group of 25 patients was submitted to the antiviral therapy. As a result, 11 patients (44%) obtained sustained virological response and among these, 45,5% obtained early
virusological response. Studies show that the procents for obtaining sustained
virusological response are slightly higher in comparisson to this study.

Regarding the antiviral therapy side effects, 14 patients (56%) presented anemia and this was associated to thrombocytopenia and leukopenia in 71,4% patients. Moreover, all patients undergoing antiviral treatment displayed flu-like symptoms during the first month of therapy. A number of 4 patients (16%) experienced depression episodes, one patient had forearm rash (4%) and 6 patients (24%) presented short episodes of dispepsia – lack of appetite, nausea and vomit. The low intensity of the symptoms did not imply the end of therapy, only the use of symptomatic treatment.

The rheumatic check-up was important throughout the entire study, both for the rheumatoid syndrome evaluation and also for the evolution of the symptoms during antiviral therapy.

At the beginning of the study, all patients presented certain modifications that are typical for the rheumatoid syndrome, such as arthralgia concerning maximum 3 joints, of various intensity; functional disability in usual movement; morning stiffness for less than 30 minutes.

Taking into consideration that there are multiple forms of arthritis associated to hepatic C viral infection [8, 9], the analysis of the affected joint showed the symmetrical involvement of medium joints as it follows: 41 patients (82%) of patients had arthralgia concerning the radiocubitocarpien joint, the metatarsophalangien joint was interested in 26 patients (52% ), the tibio-tarsal joint was interested in 10 patients 20% of patients and 8 patients (16%) had artralgia concerning the scapulohumeral joint.

Also, taking into consideration that the inflammatory process is esential for the pathology of the rheumatoid syndrome, we investigated the inflammation markers - erythrococyte sedimentation rate (ESR), C-reactive protein (CRP)- at the beginning of treatment, 3 months later and at the end of therapy by reviewing their medical charts.

Regarding Group I, a highly statistical difference was registered concerning the mean values of both parameters at the beginning of therapy, 3 months later and at the end of treatment by using both ANOVA and Kruskal-Wallis tests.
For Group II, no statistical difference was observed concerning the ESR value by using both tests. Moreover, there was no highly statistical difference concerning CRP values using both statistical tests.

Interferon-alpha is famous for its impact upon the treatment of CHC but the role of this therapy in regard to the rheumatologic manifestations associated with CHC has only recently started to be investigated.

Studies related that treatment with interferon-alpha may lead to substantial clinical improvement of HCV-related arthritis even without a complete biochemical or virusological response [10].

Although the role of IFN-alpha as an immunoregulatory molecule is not completely understood, certain data suggest that this cytokine can bring benefit to inflammatory disease due to its effect on cytokine cascade [11].

One evidence of the anti-inflammatory properties of IFN-alpha was provided by Dinarello et al who explained the reduction of IL-1 synthesis by IFN-alpha [12].

There is also proof of the induction on IL-10 by IFN-alpha, principally occured in activated CD4 cells [13]. Glisslinger et al also supported the anti-inflammatory and immunosuppressive function of IFN-alpha such as its ability to stimulate the hypothalamic-pituitary-adrenal axis in vitro and in vivo [14].

Another aspect that should be considered is the hematological impact of IFN-alpha. It was related that the administration of IFN-alpha leads to suppression of hematopoiesis in vivo [15] and in the case of inflammatory disease, this process may trigger limited supply of mature effector cells and thus a reduced inflammatory activity [11].

In our study, we suspect the immunoregulatory and anti-inflammatory activity of the IFN-alpha to have a major role in decreasing the inflammation marker levels and to improve joint symptoms in all patients belonging to group 1. Thus, the 12 month of Peg-IFNa2a/ribavirine combined treatment diminished arthralgia, morning stiffness and functional disability and also the CRP and ESR levels, in comparison to the control group who was not submitted to antiviral therapy.
CONCLUSIONS

The study included a total of 50 patients diagnosed with chronic hepatitis C and rheumatoid syndrome which were divided in two groups. The first one contains 25 patients who underwent Peg-IFNα2a/ribavirine antiviral therapy and were compared to the rest of patients who refused the treatment.

We statistically evaluated the common anamnestic particularities of 50 patients with chronic hepatitis C and rheumatoid syndrome which are important in order to better understand the clinical profile of these patients for an early diagnose and treatment onset.

The following parameters were considered: age, sex, environment, body mass index, hepatitis C risk factors for the studied group, onset rheumatological symptoms, liver function medical investigation elements for the patients who would initiate the antiviral therapy.

The study shows that when administrated to patients with chronic hepatitis C and rheumatoid syndrome, Peg-IFNα2a/ribavirine associated with low dose of NSAID can positively influence the rheumatological symptoms. Thus, using this combination for a period of 12 months diminished arthralgia, morning stiffness and functional disability that were the main complaints of these patients.

On the other hand, this drug combination offers obvious benefit to the inflammation markers, their profile considerably improving at the end of the study period, in comparison to the group of patients who was not submitted to the antiviral therapy.

Last but not least, despite the typical side effects, the therapy was well tolerated and there were no voluntary or side effect related interruptions of treatment. The Peg-IFNα2a/ribavirin therapy proved to be useful for the rheumatoid syndrome, with no negative immune mediated effect or negative impact upon the joint symptoms.
References

