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2nd International Conference on Gastroenterology & Urology: The risk of therapy with interferon and ribavirin - Manuela Stoicescu - University of Cluj Napoca, Romania

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Objectives: The main objective of this clinical case presentation is to attract attention to the risk of therapy with interferon and ribavarin. Materials & Method: I present the clinical case of a woman patient 44 years old, who came to consult for asthenia, after following a diet for weight loss. The objective examination was within normal limits except the presence of a hepatomegaly at 1, 5 cm under the last rib, with regular border, increase consistence, regular surface, without pain at the time of palpation. The laboratory examination showed: ALT=48 UI/l, ALP=56 UI/l, total bilirubin=1,8mg/dL, indirect bilirubin=1,5 mg/dL, direct(conjugated) bilirubin=0,3 mg/dL, Gamma GT=58 UI/L, FA=36 UI/L, serum protein=7.2 g/100 ml, serum protein electrophoresis albumin=28% α1=4% α2=6% β=10% γ=21%, serum immunoglobulin levels: IgG=720 mg/100 ml, IgM =96 g/100 ml, IgA=90 mg/100 ml, TS=1,2s, TC=1,4s. After I performed a test for viral markers it appeared Anti-HCV positive, Hepatitis B virus (HBV) negative, an Anti-mitochondrial antibodies negative, viremia=5 000 000 IU/ml. At this moment I established the diagnosis; active chronic virally C hepatitis positive. Abdominal eco confirmed hepatomegaly with increased echogenity and normal portal vein=11mm. After that the patient performed a needle hepatic biopsy which showed the histopathological diagnosis of? peace meal necrosis?. Results & Discussions: It is possible that therapy with interferon and ribavarin can have cancer risks, which we don?t know actually at present. It is also possible for changes to appear in the autoimmune system of the body modifying the reaction of the body to different drugs, such as Penicillin G in the situation presented. Conclusions: Women patients after standard protocol with Interferon and Ribavarin must to be screened followed by mammography for early discovery of breast cancer and also other cases reported, which probably will be contraindicated in the future, this routine therapy used in the present for treatment of the patients who are virus C and B positive. Also we must be careful of the reaction of the drugs after this therapy because it is possible for the patient to develop very severe allergic reactions which put their lives in danger. I think at this moment we don?t know all the dangerous side effects of this therapy with interferon and ribavarin and in the future there are possible changes with other drugs. The risks of side effects compared with benefits must be seriously taken into account.

Ribavirin, also known as tribavirin, is an antiviral drug used to treat RSV, hepatitis C and some hemorrhagic fevers. It is used in conjunction with other drugs for hepatitis C, such as simeprevir, sofosbuvir, peginterferon alfa-2b, or peginterferon alfa-2a. Ribavirin is used to treat chronic (long-lasting) hepatitis C, a viral infection of the liver in conjunction with other antiviral drugs (such as interferon, sofosbuvir). Infection with chronic hepatitis C can cause severe liver complications, such as scarring (cirrhosis), or hepatic cancer. Ribavirin works by reducing the body's amount of hepatitis C virus which can help the liver heal.

Ribavirin is a synthetic guanosine nucleoside and antiviral agent that interferes with the synthesis of viral mRNA, producing a broad-spectrum activity against many RNA and DNA viruses. This is recommended specifically for use in treatment of hepatitis C and hemorrhagic viral fevers. HCV is a single-stranded RNA virus classified into nine distinct genotypes, with Genotype 1 being the most prevalent in the United States, affecting 72 per cent of all chronic HCV patients 9. Ribavirin is confirmed to be effective only in the early stages of viral hemorrhagic fevers, including Lasser fever, Crimean-Congo hemorrhagic fever, Venezuelan hemorrhagic fever, and Hantavirus. Ribavirin is a prodrug that is metabolized into nucleoside analogs which blocks the synthesis of viral RNA and the capping of viral mRNA. Ribavirin and Peginterferon alfa-2a / Peginterferon alfa-2b dual

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therapy is considered the first-generation and normal antiviral therapy 5 prior to the development of newer drugs. Dual therapy in patients with genotype 1, 4, 5, and 6, and 24 weeks in patients with genotype 2 and 3 5, was performed for 48 weeks. New medications developed as treatments for viral hepatitis C infection may be used to minimize or replace the use of ribavirin, which is associated with significant adverse effects.

Ribavirin is reported to have several mechanisms of action leading to a viral RNA inhibition and protein synthesis. After activation of mono- , di-, and triphosphate metabolites by adenosine kinase to ribavirin. Ribavirin triphosphate (RTP) is the predominant metabolite which inhibits viral mRNA polymerase directly by binding to the enzyme's nucleotide binding site. This prevents the binding of the required nucleotides, resulting in decreased viral replication or manufacturing of faulty virions. RTP also demonstrates an inhibitory effect on the dengue virus virus mRNA guanylyltransferase and mRNA 2′-O-methyltransferase. Inhibition of these enzymes disrupts the posttranslational capping of the 5′ end of viral mRNA through ribavirin being incorporated at the 5′ end in place of guanosine and preventing the cap methylation step.

Inhibition of these enzymes interferes with the post-translational capping of the 5′ end of viral mRNA via the incorporation of ribavirin at the 5′ end instead of guanosine and prevents the step of cap methylation. Another mechanism for ribavirin's action is suggested to be inhibition of host inosine monophosphate dehydrogenase (IMPDH) and subsequent depletion of GTP reservoir. IMPDH catalyzes the rate-limiting step in which 5′-monophosphate inosine is converted into xanthine monophosphate during the synthesis of guanosine monophosphate (GMP). GMP is later transformed to the triphoshpate guanosine (GTP). Ribavirin monophosphate imitates 5′-monophosphate inosine, which functions as a powerful IMPDH inhibitor. Inhibited de novo synthesis of guanine nucleotides and decreased intracellular GTP pools leads to a decline in viral protein synthesis and limit replication of viral genomes.

Owing to increased viral mutations, ribavirin functions as a mutagen in the target virus to cause a 'error catastrophe." RTP pairs equally effectively with cytidine triphosphate or uridine triphosphate and to block elongation of HCV RNA. It causes the nascent HCV RNA to stop prematurely and enhances mutagenesis by creating defective virions. Also, ribavirin exerts the host's immunomodulatory action on the virus by transferring a Th2 response to a Th1 phenotype. Type 2 cytokines such as IL-4 , IL-5, and IL-10 reaction and development of Th2 activates the humoral response that enhances immunity to virus. Ribavirin enhanced induction of interferon-related genes, including the interferon-α receptor, and down-regulation of genes involved in interferon inhibition, apoptosis, and hepatic stellate cell activation in vitro.

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