Contribuições de monitoramento da farmacoterapia com peginterferon e ribavirina em um paciente com hepatite C crônica

Contributions of peginterferon and ribavirin pharmacotherapy monitoring in a chronic hepatitis C patient

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RESUMO

INTRODUÇÃO: O tratamento da hepatite C através da terapia combinada com peginterferon e ribavirina visa interromper a progressão da doença inibindo a replicação viral. Devido à eficácia terapêutica combinada com reações adversas, esses medicamentos denotam indicações e contra-indicações específicas. OBJETIVO: O objetivo do presente estudo foi acompanhar a resposta virológica apresentada por um paciente com diagnóstico de hepatite C em estágio inicial, monitorando a farmacoterapia e as reações adversas. MÉTODO: O estudo consistiu em estudo descritivo e qualitativo de um paciente, no qual foram analisados por 11 meses exames laboratoriais, medicamentos prescritos por médicos, relatórios fornecidos pelo paciente sobre os sintomas apresentados e a descrição da evolução da doença. Análise de um mês antes do início do tratamento e um mês após a conclusão do tratamento também foi considerada para contagem de leucócitos, plaquetas, quantificação de hemoglobina e TSH. A massa corporal do paciente foi monitorada antes, durante e oito meses após o tratamento. RESULTADOS: Foram observadas reações adversas hematológicas e endócrinas moderadas, como: leucopenia, diminuição da contagem de plaquetas, hipohemoglobinemia, diminuição da função tireoidiana e perda de peso. DISCUSSÃO: Embora reações adversas tenham sido identificadas, a resposta virológica sustentada foi alcançada durante o tratamento, comprovando eficácia terapêutica. Esse fato foi possível devido ao monitoramento do paciente, reajuste da dose e acompanhamento clínico durante 11 meses de tratamento. Enfatizamos a necessidade de acompanhamento para analisar a relação benefício/risco da farmacoterapia, adesão ao tratamento e garantia de segurança ao paciente.

Palavras-chave: Hepatite C. Ribavirina. Peginterferon. Terapia medicamentosa. Efeitos colaterais relacionados a medicamentos e reações adversas.

ABSTRACT

INTRODUCTION: Treatment for hepatitis C through peginterferon and ribavirin combination therapy aims to halt disease progression by inhibiting viral replication. Due to their therapeutic efficacy combined with adverse reactions, these drugs denote specific indications and contraindications. OBJECTIVE: The objective of the present study was to follow up the virological response presented by a patient diagnosed with early stage hepatitis C by monitoring pharmacotherapy and adverse reactions. METHOD: The study consisted in descriptive and qualitative study of a patient, in which laboratory tests, prescriptions of medications prescribed by physicians, reports provided by the patient about the symptoms presented and the description of the evolution of the disease were analyzed for 11 months. An analysis of one month prior to treatment initiation and one month after treatment completion was also considered for leukocyte count,

platelets, hemoglobin quantification and TSH. Patient's body mass was monitored before, during and eight months after treatment. RESULTS: Moderate haematological and endocrine adverse reactions such as leukopenia, decreased platelet count, hypohemoglobinemia, decreased thyroid function and weight loss were observed. DISCUSSION: Although adverse reactions have been identified, sustained virological response was achieved during treatment, proving therapeutic efficacy. This fact was possible due to patient monitoring, dose readjustment and clinical follow-up over 11 months of treatment. We emphasize the need for follow-up to analyze the drug benefit / risk ratio, treatment adherence and patient safety assurance.

Keywords: Hepatitis C. Ribavirin. Peginterferon. Drug therapy. Drug-related side effects and adverse reactions.

INTRODUCTION

There are an estimated 71 millionpeople worldwide chronically infected with the hepatitis C virus (HCV). In Brazil2.5% to 4.9% of the population is infected. However, around the world just 7% had started the effective treatment in 2015 (WHO, 2017). Hepatitis C is considered the leading cause of liver disease and liver transplantation in the United States, and may progress to cirrhosis (20% to 40% of cases) and hepatocellular carcinoma (2.5% of cases) (ACRAS *et a*l., 2004; DOYLE *et a*l., 2012; EASL, 2017).

The risk factors strongly associated with infection are: injection drug use (WILLIAMS *et al*., 2011; SOUTO *et a*l., 2012) blood transfusion prior to the introduction of the research of anti-HCV in blood donors, to a lesser extent, puncture accident (ALVES *et a*l., 2003) and sexual transmission. Among this ways for hepatitis C transmission, the possibility of sexual transmission have to be emphasized because of the contamination rates of sexual partner that varies from 6 to 10% (STRAUSS, 2001; EASL, 2017).

Other forms of contamination are the medical and dental procedures so as acupuncturist or tattoo. Therefore, any sharp or piercing can be vehicle transmitter of the virus from one person to another, such as the manicure pliers, the blade of the barber or even tooth brush, shared by the spouse or children. In cases where departs the hypothesis of blood transfusion or use of illicit drugs, there was a significant percentage of patients with prior surgery and/or prior consultations of urgency in ready-aid or the hypothesis confirmed medical contamination during the surgical procedure (RODRIGUES NETO *et a*l., 2012).

One of the notable features of the HCV is the ability to evade the immune system of the infected host. Viraemia persists in 85% -90% of the infected individuals, approximately 70% of whom develop some degree of chronic liver injury and the potential to progress to cirrhosis and hepatocellular carcinoma. The exact time course of hepatitis C remains unknown, due to the difficulty of defining the beginning of the infection and the multiplicity of co-factors able to influence its progression. Differences in the evolution of chronic infection of each patient must be related to viral and host factors. Such variables could lead to heterogeneous clinical evolution of the disease, as slow progression or even absence of it (VASCONCELOS *et a*l., 2006).

Detection of anti-HCV antibodies can be initially by methods of high sensitivity (100%) and specificity (99.84%), by the enzyme immune assay (ELISA) and microparticle enzyme immune assay (half), which employ synthetic peptides of HCV. Subsequently, the results obtained must be confirmed by methods of high specificity, like recombinant immunoblot assay (RIBA) or Western Blot (WB) so as the viral ARN detection by polymerase chain reaction (PCR) and qualitative and quantitative techniques of

deoxyribonucleic acid (DNA) -branched (routines). The RIBA has the inconvenience of presenting about 10% to 20% of indeterminate or inconclusive results (PALTANIN, REICHE, 2002).

The use of interferon is currently the only approved therapeutic modality by the FDA (Food and Drug Administration) for the treatment of hepatitis C, whether through its use in the form of monotherapy (interferon alpha or peginterferon) or associated with drugs such as ribavirin. By the end of the 90's was intensified in Brazil the association between interferon and ribavirin in treatment of chronic HCV infection, including free distribution of medication in certain regions of the country (ÁVILA *et al*., 2006; ALMEIDA *et al*., 2009).

The interferons belong to the superfamily of cytokines. Such molecules modulate the activity of many components of the immune system, increasing the body's ability to fight infectious agents. They are classified into alpha, beta and gamma, according to their amino acid sequence. Interferon-alpha is produced by monocytes and B cells in response to viruses and antigenic stimuli. The recombinant interferon is produced by recombinant ADN techniques in *Escherichia coli*. Two forms of recombinant interferon-alpha are commercially available and differ by a single amino acid at position 23: lysine in interferon-alpha-2A and arginine in interferon-alpha-2B.

Pegylated interferon or peginterferon is a form of interferon that has a prolonged action (more than 8 hours with conventional interferon because it has been modified by the addition of a polyethylene glycol molecule. Its administration is weekly and when compared with conventional interferon, the results of the therapy are superior. For this reason, and because conventional interferon needs to be administered subcutaneously 3 times, its use is less and less. Therefore, this characteristic is considered beneficial for pharmacotherapeutic adherence in a patient with hepatitis C, since the treatment is long. The ribavirin is a synthetic nucleoside analog (guanosine). Selectively inhibits the synthesis of ADN, ARN and viral proteins in infected host cells and improves the immune response mediated by cytokine against viruses, more specifically interleukin 2 (IL-2), tumor necrosis factor alpha (TBF-alpha) and interferon-gamma by CD4 and CD8 T lymphocytes. This drug also has a long half-life, allowing the association with pegylated interferon, as well as therapeutic convenience (CAVALCANTI, PARANÁ, 2006; BIDELL *et al*., 2016; SATOH *et al*., 2017).

It is worth recalling that in 1990s, interferons alpha-2 were used in the treatment of HCV and in the next decade HCV therapy was based on pegylated interferon alpha-2 in combination with ribavirin, because the monotherapy in the before decade showed rapidly developing viral resistance (ZAJAC *et al*., 2019).

Although we have already approved other treatments since 2011, treatment monitoring in the past decade allows us to know the safety and efficacy of peginterferon associated with ribavirin, signaling the maintenance of this treatment in clinical protocol today, for children aged 3 to 11 years (BRASIL, 2019) ;as well as enabled the knowledge of new therapeutic strategies.

The present work aims to identify the therapeutic response to hepatitis C with peginterferon and ribavirin, performing therapeutic monitoring in a patient. In addition, was discussed the adverse reactions profile in a patient diagnosed at the initial stage of the disease and under treatment.

METHODS

The work consisted of descriptive and qualitative study of a case, in which the laboratory examinations carried through by the patient, the medical

prescriptions, the experiences supplied by the patient on the symptoms presented for the illness and the description of the evolution of it have been analyzed, comparing with existing literature. The patient received a "Term from Free and Clarified Assent", with clarifying character regarding to be carried through research. After the clarification of the objective of the research and fulfilling of the "Term of Free and Clarified Assent", as well as approval for the Committee of Ethics (protocol n.° 161568/2007) at the *Universidade Nove de Julho*, the work had beginning.

The pharmacotherapeutic monitoring plan consisted in knowledge about biochemical patient data before and during the established treatment. We considered the body weight patient during and after the treatment. All monitoring lasted nineteen months to the body weight and twenty months to the biochemical data. The month zero consisted in pre-treatment to identify the biochemical data about: hemoglobin dosage, thyroid stimulating hormone (TSH) quantification, leukocyte and platelet count. The patient was not submitted to the leukocyte count in the month two; platelet count in the months two, seven and eight; hemoglobin dosage in the months two and seven; TSH quantification in the months two, five, seven and eight. The treatment was established with subcutaneous peginterferon and oral ribavirin during eleven months. The prescribed pharmacotherapy was 2 oral pills of ribavirin 250 mg every 12 hours associated with subcutaneous peginterferon alpha 2B once a week (see Table I). The viral load (U/mL) was quantified by qPCR at the beginning and end of the treatment. Adverse reactions reported by the patient were noted, some of which hematological and endocrine in nature were monitored by biochemical analysis.

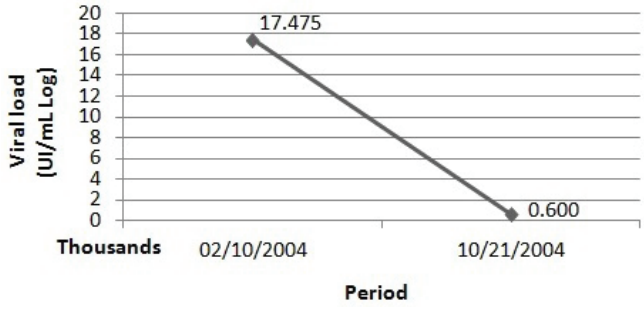

FIGURE 1. Viral load reduction after 8 months of treatment with pegylated interferon and ribavirin. The viral load (U/mL) in thousands, was quantified by qPCR at the beginning and end of the pegylated interferon and ribavirin treatment.

RESULTS

The result of the quantitative PCR for HCV presented initial viral load of 17.475 UI/ml and genomically classified as 1B (as demonstrated in Figure 1). It was requested a liver biopsy (left lobe) in which the macroscopic examination consisted of a phyliform fragment, measuring 1.6 cm of length and 0.1 cm of diameter, constituted by elastic-brown tissue. The liver presented conserved aspect and architecture, with absence of any signal of portal hypertension, being diagnosed chronic hepatitis for "C" virus with the following characteristics: structural alterations with portal fibrosis, slightly density of the portal inflammatory infiltrate periportal, activity with

Table I. Dosage of pegylated interferon prescription. Pegylated interferon dose and volume of administration on every time-point during the treatment.

Month of treatment	Pegylated interferon alfa 2B (1.5 µg/kg)	Volume (mL)
1°	100	0.52
2°	100	0.51
3°	100	0.52
4° to 6°	80	0.65
7°	80	0.64
8° and 9°	80	0.60
10°	80	0.62
11°	80	0.60

slight necroses in "bag-bits" format in small areas, parenchymatic activity with slight hepatocyte necroses in several sites, etiological markers like steatosis and lymphoid aggregates.

The adverse reactions, described by the patient and verified through laboratory exams, upon the alpha ribavirin and peginterferon 2B use were described in Table II.

Table II. Adverse effects during pegylated interferon and ribavirin treatments.

DRUGS	ADVERSE EFFECTS
Pegylated interferon alfa 2B	Flu symptoms: fever, myalgia and headache. Gastrointestinal disorders: nausea and diarrhea. Neuropsychiatric symptoms: tiredness, irritability and depression. Myelossupression dose-dependent: neutropenia, thrombocytopenia and mild anemia. Endocrine disorders: mild hypothyroidism. Dermatological disorders: hair loss, skin rash and psoriasis.
Ribavirin	Dose-dependent hemolytic anemia. Nonspecific effects: fadigue, headache, insomnia, depression, coughing.

Throughout the treatment, it was possible to detect through accompaniment examinations hematological alterations like leukopenia (see Figure 2), decreased platelet count (see Figure 3), discrete anemia (see Figure 4) as well as TSH levels reduction (see Figure 5). Body weight was also monitored (to see Figure 6), demonstrating a reduction body weight during the treatment.

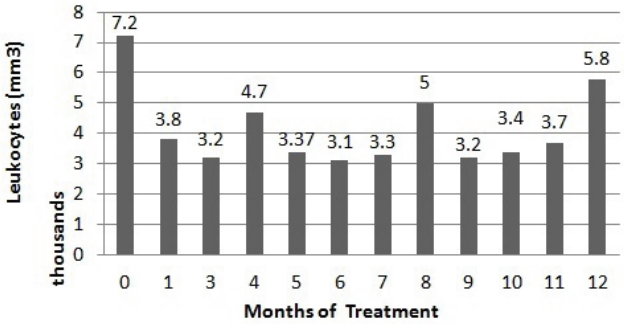

FIGURE 2. Evaluation of leukopenia during pegylated interferon and ribavirin treatment. Leukocytes count (leukocytes/mm3) in thousands, were determined in each month of treatment; initial (before treatment) leukocytes count is represented by month 0. The reference minimum value is 4, 000 leukocytes per mm3.

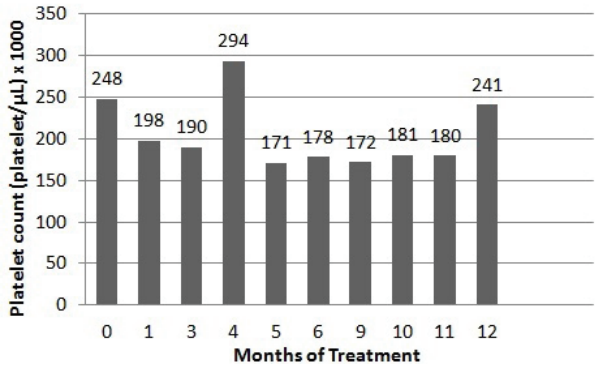

FIGURE 3. Evaluation of platelet count during pegylated interferon and ribavirin treatment. Platelet count (platelet/µL) (in thousands) were determined in each month of treatment; initial (before treatment) platelet count is represented by month 0. The reference minimum value is 140, 000 platelet/µL.

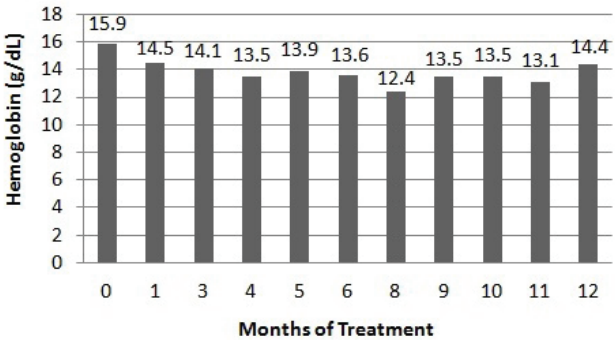

FIGURE 4. Evaluation of hemoglobin during pegylated interferon and ribavirin treatment.Hemoglobin (g/dL) was determined monthly with month 0 as the hemoglobin dosage pre-treatment. The reference minimum value is 13.5g of hemoglobin per dL.

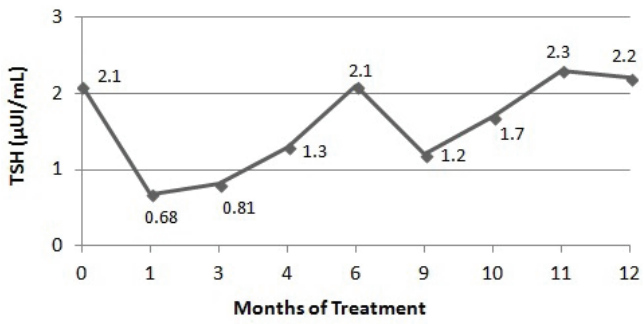

FIGURE 5. Evaluation of thyroid gland function during pegylated interferon and ribavirin treatment.Thyroid gland function was evaluated by TSH quantification (µU/mL) monthly during the treatment. Reference value 0.3 to 4.20µU/mL.

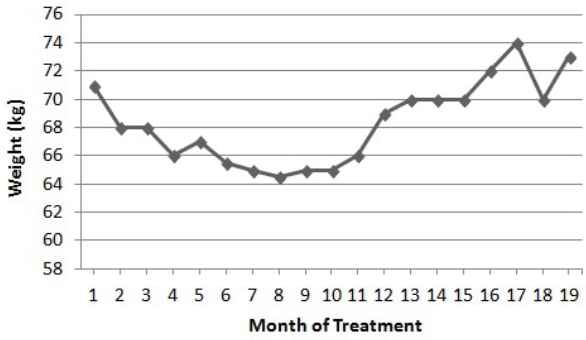

FIGURE 6. Body weight monitoring during pegylated interferon and ribavirin treatment.Patient weight was monitored until 8 months after the end of the drugs treatment (11th month).

DISCUSSION

In this clinical case was detected the 1b viral genotype. Excellent virological response was gotten after 5 months of the beginning of the therapy with peginterferon and ribavirin with complete response after the ending of the treatment, that is, the evaluation as soon as the treatment ends was defined as ARN-HCV negativation. According to Strauss (2001) the maintained response represents the maintenance of complete response during a more than 6 months period after the interruption the treatment. Because of the medical habit, it was carried out the 6-month period accompaniment of the viral load of the patient until the end of the treatment 3 years after, where the patient did not present viral return in this period, and the sustained response was achieved. These data are not corroborated by the literature, where, taking into account the genotype, the most frequent of them - 1b, is admittedly that one with worse therapeutically response. The initial studies associated the 1b genotype with more frequent evolution for cirrhosis and hepatocarcinoma. The 1b genotype was associated with advanced age patients, with long lasting infected patients or in the patients with illness acquired for blood transfusion (KRYCZKA *et al*., 2001; ACERO FERNANDÉZ *et al*., 2018). However, in the presented case, the viral infection by the 1b genotype is excluded from the cited associations, because according with the medical diagnosis, the initial viral load of the patient signalized a recent infection and the patient do not participate of transfusion proceedings and presented an optimal virological response.

Weekly administration of peginterferon 2B alpha prescribed coincides with the described one in literature, because the new developed form of interferon, called pegylated interferon or peginterferon, consists of the addition of a polyethylene glycol molecule to the interferon molecular structure. Because of its bigger structure, interferon it is more hardly metabolized, allowing its sanguineous dosages remain high for longer time periods. The biological activity of interferon remains qualitatively unchanged and its administration, instead of three times per week, starts to be weekly (ÁVILA *et al*., 2006).

The attainment of the viral response after the 20th week of treatment, with reduction of the initial viral load of 17.475 UI/mL to < 600 UI/mL shows a striking amelioration after the treatment of chronicle hepatitis C with the combination of peginterferon alpha 2B and ribavirin. Studies had demonstrated, with the

isolated use of interferon, effectiveness in about 50% of the cases, percentages that must increase with the combination of interferon and ribavirin (STRAUSS, 2001; FELD *et al*., 2007; KEAM, CVETKOVIĆ, 2008). However it must be detached that in the conventional administration of interferon, occurrence of great fluctuations in the serum concentrations exists, resulting in peak/valley ratio (ratio between the maximum and minimum concentration) infinite. There are periods where the medicine is not in the circulation; therefore, the viral suppression is not kept, being able to occur the turn back of the original viral concentration (BAILON *et al*., 2001). This fact is not observed in the use of peginterferon, because once in the circulation, it is predominantly distributed in the sanguineous current and the interstitial fluid, but not on the tissues, mainly in perifused organs like the liver. The concentration equilibrium is maintained during the whole administration period that must be of 48 weeks (REDDY *et al*., 2001). We highlight then the high therapeutic effectiveness of peginterferon in relation to the therapy with conventional interferon, assuming that the presented data confirm the described in the literature, in which is an increase of the effectiveness of the combined interferon and ribavirin treatment, being that the effectiveness still can be bigger when if uses the new form of interferon, peginterferon (BEZERRA, OLIVEIRA, 2007).

The therapy positive effect is usually accompanied with adverse effects (KOSTIĆ *et al*., 2012; MINAMI *et al*., 2013). A series of adverse events was associated with the use of peginterferon and ribavirin, in which peginterferon presented, separately, greater adverse effect. Interferon leads to adversereactions in many organs (DONNELLY *et al*., 2011). The flu symptoms, like fever, myalgia (PREDESCU *et al*., 2012), migraine and gastrointestinal alterations like nauseas and diarrhea had been more intense in the first doses of the medication, being mitigated throughout the treatment. However, as described in the literature (KOSTIĆ *et al*., 2012) these symptoms disappear after the suspension of the medication.

It is well known that leukocytes are the defense of the organism against infectious agents and strange substances, to defend the body adequately, and an enough amount of leukocytes must stimulate the appropriate immunological responses. The reduction of white globules can be related with viral infection, however the use of some medicines can lead to the fall of leukocytes. In this study, it was possible to perceive that the adverse effect of myelosuppression for the use of the peginterferon provoked the leucopenia, therefore was notable the fall of the number of leukocytes after the beginning of the treatment. There is also the association fever with leukopenia presented by the patient, since some of the leukocytes are involved in small inflammatory processes.

Another adverse reaction related to the peginterferon was the reduction of the number of platelets after the beginning of the treatment. According to Vasconcelos (2006) in patients with chronic hepatic illness and portal hypertension, the plateletopenia is in part debt of the splenic kidnapping of the platelets. The low level of thrombopoietin produced by the liver is another responsible factor for such finding.

The clinical studies had contributed to confirm the hypothesis that the main collateral effect of ribavirin is the hemolytic anemia that develops in the first weeks of the drug administration (SAITO *et al*., 2006; KRISHNAN, DIXIT, 2011; MOLINA-CUADRADO *et al*., 2018). According to Jarvis and collaborators (1998), this is debt to the greater permanence of the drug in the erythrocytes; because of the absence of nucleus in these cells they become slow on the phosphorylation necessary for the drug elimination, conducting to extravascular hemolysis. Because of the dose-dependent nature of this adverse effect, according with the clinical case of the patient, it was

not necessary the suspension or reduction of the dose, because of the discrete anemia presented, that is, the hemoglobin levels had remained next to the value of reference. In accordance with Strauss (2001) and Rosa (2011), it is necessary the readjustment of the dose or its suspension in case that hemoglobin falls below of 10g%.

Because of its lymphotropism, the HCV can represent a stimulus for the immune system taking to a series of autoimmune illnesses like thyroiditis, condition also found during the alpha treatment with interferon (aIFN), therapy frequently used in hepatitis C (FAIS *et al*., 2001; TRAN *et al*., 2011; BARUT *et al*., 2012). Several authors like Bianchi and collaborators (1991) and Green and collaborators (1977) suggest abnormalities of the thyroid function in association with hepatic illnesses in all the levels of the hypothalamus-hypophysis-thyroid axis, as well as in the transport and peripheral metabolism of thyroid hormones. In these cases there are a multiplicity of involved factors, amongst which, the type and degree of malnutrition and hepatic function with presence or not of inflammatory activity is a common one. Aftermath confirmed by other investigators like Chang and collaborators (2019), disturbs of the thyroid gland are common abnormalities in patients with chronicle hepatitis C, exactly before the beginning of the treatment with interferon. Between these disturbs, is the primary hypothyroidism in 3.1 to 5.5% of the patients, most of the time as resulted of autoimmune thyroiditis. On the present case we found positive association with the data of literature, however in this study we show that the patient presented a fall in TSH hormone, however, without reaching the minimum value of reference. The figure 5 shows that the fall of the hormone occurred after the beginning of the drug therapy. We can then associate this fact to the use of the peginterferon drug, therefore the patient presented normal values of TSH before the beginning of the treatment and, as observed in literature, peginterferon use present a characteristic undesired endocrine reaction, like hypothyroidism.

Beyond the related described adverse reactions with the prescribed medicines, it also had the report of the appetite lack, not being possible to relate it with one of the used drugs, however this fact took to the loss of weight presented in figure 6, that it can be associated to the neuropsychiatric effects like depression (HASSAAN *et al*., 2019), in which was a notable manner alteration of the patient. Kostić and collaborators (2012) also identified weight loss related with insomnia and irritability, considered later manifestations. No pharmacokinetic interaction between pegylated interferon and ribavirin was observed in the clinical studies in progress, in which peginterferon is used in combination with ribavirin (KOROLKOVAS, FRANÇA, 2017).

Peginterferon has antiviral effect by inhibiting the viral proliferation and hindering the infection of non-infected so as by its antiproliferative action (NADAL *et al*., 2003). It was described that the drug binds to specific cellular membrane receptors, inducing the activity of determined enzymes, inhibiting the cellular proliferation (KOROLKOVAS, FRANÇA, 2017). In this context, taking into account that this drug inhibits cellular proliferation, it affects too the division of the hair follicle, characterized for intense proliferative activity. In consequence produce the loss of hair, one of the adverse events stated by the patient.

The alpha interferons can affect the oxidative metabolic process reducing the activity of hepatic microsomal enzymes of cytochrome P450 (CYP450). There are evidences that ribavirin and interferon cause lower hepatic CYP2D6 and CYP3A4 activities during 1 month of the treatment. In consequence, the potential degree of interaction of ribavirin with the P450 enzymes is relevant (BECQUEMONT *et al*., 2002).

The sustained response rate in this study was superior to the informed in literature, due to the worst

virologic responses for all the genetic variants of the virus is the 1b, the one presented in this work. The pathology did not envolve for the hepatocarcinoma and cirrhosis scenario. Because of the complete response with the negativation of the HCV-ARN and a sustained response 3 years after the treatment, could be concluded that the combined peginterferon and ribavirin therapy is effective.

Currently, among the new direct action antivirals proposed for the treatment of hepatitis C, the following drugs are available on the Brazilian market with approval from Anvisa: sofosbuvir, a nucleotide analog that inhibits HCV polymerase; simeprevir, a protease inhibitor of second generation; daclatasvir, an inhibitor of non-structural protein 5A (NS5A) and the combination of ombitasvir viral targets, veruprevir, ritonavir and dasabuvir. Sofosbuvir today represents a treatment of choice associated with daclatasvir or ledipasvir in two therapeutic options in the current clinical protocol for hepatitis C with genotype 1b in adults. These drugs have better therapeutic comfort, as they are administered orally, in the form of tablets, once a day. In addition, sofosbuvir has a high genetic barrier to resistance viral and resistant variants of HCV. Given the above, it represents the main treatment today. However, peginterferon and ribavirin associated remain in use for children aged 3 to 11 years, subcutaneously once a week, for 48 weeks (SBI, SBH, 2016; BRASIL, 2019).

CONCLUSION

Finally, considering the high number of adverse reactions presented by the drugs, we strengthen the importance of the pharmacological accompaniment and the pharmaceutical attention in order to guarantee the adhesion to the treatment and the clarification of that the success of the treatment lies in the continuing of it for the indicated period. The presented collateral effect must be notified so that makes possible the treatment, aiming at the welfare of the patient, either carrying through maintenance of doses or inclusion of therapeutic measures that eliminate the inconveniences caused for the treatment.

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STATEMENT OF CONFLICT OF INTEREST

There is not.