

# Pulmonary manifestations associated with the current treatment of chronic hepatitis C

## *Manifestações pulmonares associadas ao tratamento atual da hepatite C crônica*

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### ABSTRACT

Hepatitis C is a major global public health problem, with a global prevalence average of about 3%. The majority of infected individuals (70%) develop chronic hepatitis and liver cirrhosis. Currently, two agents, pegylated interferon (PEG-INF) and ribavirin, have been employed in the treatment of chronic hepatitis C infection. Side effects and adverse events attributed to treatment of chronic hepatitis C with pegylated interferon and ribavirin have recently been better understood. Pulmonary abnormalities have been described with the use of these drugs and range from mild to potentially severe. Considering the increasingly frequent use of interferon in hepatitis C and other diseases, this review aims to assist in the early detection of lung side effects of this drug, as well as their proper management.

**Key words:** *Hepatitis C; Hepatitis C/therapy; Lung Diseases; Interferons/adverse effects; Ribavirin/adverse effects.*

### RESUMO

*A hepatite C é dos principais problemas mundiais de saúde pública da atualidade, com prevalência global média próxima de 3%. A maioria dos infectados (70%) desenvolve hepatite crônica e cirrose hepática. Atualmente, dois agentes, o interferon peguilado (PEG-INF) e a ribavirina, têm sido empregados no tratamento da hepatite C crônica. Os efeitos colaterais e eventos adversos atribuídos ao tratamento da hepatite C crônica com interferons peguilados e ribavirina vêm sendo mais bem reconhecidos na atualidade. Alterações pulmonares têm sido descritas durante o uso dessas drogas e variam com manifestações desde leves a potencialmente graves. Considerando o uso cada vez mais frequente do interferon na hepatite C e em outras doenças, esta revisão objetiva auxiliar no pronto reconhecimento dos efeitos colaterais pulmonares dessa droga, assim como o seu adequado manejo.*

**Palavras-chave:** *Hepatite C; Hepatite C/terapia; Pneumopatias; Interferons/efeitos adversos; Ribavirina/efeitos adversos.*

### INTRODUCTION

Hepatitis C is currently a major global public health issue<sup>1,2</sup>, with the global prevalence averaging close to 3%<sup>3-6</sup>. The hepatitis C virus (HCV) is responsible for 20 and 70% of cases of acute hepatitis and chronic hepatitis and liver cirrhosis, respectively, considering that cirrhosis constitutes the main indication for liver

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transplant.<sup>7</sup> It is estimated that 150-200 million people are carriers of HCV worldwide<sup>3,4</sup> and two to three million in Brazil.<sup>8,9</sup>

Treatment of chronic hepatitis C caused by HCV aims to eradicate the etiologic agent in order to interrupt the inflammatory and fibrotic process in the liver and to prevent the development of liver cirrhosis and hepatocellular carcinoma. Two agents, interferon alpha (IFN- $\alpha$ ) or PEGylated interferon (PEG-INF) and ribavirin are used in the treatment of chronic hepatitis C.<sup>5,10,11</sup>

IFN- $\alpha$  is an antiviral with potent immunomodulating effects. Combining a polyethylene glycol molecule with IFN- $\alpha$  via a covalent bond (PEGylation) IFN- $\alpha$  results in modified half-life and longer duration of action, which optimizes both distribution and drug absorption. Combined use of PEG-INF and ribavirin is more efficient than the combination of IFN- $\alpha$  and ribavirin, or PEG-INF alone, and is the treatment currently recommended for patients suffering from chronic hepatitis C and genotype 1.<sup>12</sup>

Several adverse effects have been attributed to treatment with IFN- $\alpha$ , with or without associated ribavirin, including flu-like symptoms such as fever, malaise, and headache, as well as weight loss, alopecia, bone marrow suppression, and psychiatric disorders. It has been described that certain autoimmune diseases may be triggered by IFN- $\alpha$  including thyroiditis, autoimmune hepatitis, idiopathic thrombocytopenic purpura, rheumatoid arthritis, and systemic lupus erythematosus.<sup>13-17</sup>

Pulmonary complications are also described during the use of IFN- $\alpha$ , mainly in the first weeks of treatment. Clinical status is changeable, with mild symptoms including cough, dyspnea, and fever, which rarely evolve into severe hypoxemia. Nevertheless, in most cases, pulmonary toxicity attributed to IFN- $\alpha$  is reversible upon discontinuation of therapy.<sup>18,19</sup>

Bearing in mind the increasingly frequent use of interferon in hepatitis C and in other diseases, pulmonologists and other physicians involved in the treatment of those patients should be able to recognize the drug's side effects as well as how to adequately handle them.

In this review we will present the main pulmonary manifestations that can occur during the treatment for hepatitis C. In order to understand better the pathogenesis of those alterations, a brief review will be made on the mechanism of action of the drugs used in the treatment of hepatitis C, important basis for better understanding the mechanisms of toxicity and pulmonary symptoms.

## INTERFERON ALPHA AND RIBAVIRIN ACTION MECHANISMS

### Interferon alpha

IFN is a natural non-glycosylated serum protein, with 19 kilodaltons, found in serum at nanomolar concentrations. It is produced by exposure to foreign antigens and viral infections, including HCV. A larger production of IFN aims at modifying the function and feasibility of infected cells, inducing responses of the cellular innate immune system and directing the adaptive immune response to the Th1 phenotype, intended to eradicate the infectious process. Recent evidence suggests that IFN- $\alpha$  plays a fundamental role in the chemotaxis of NK cells and macrophages to the liver infected with a virus.

Conventional IFN- $\alpha$  and PEG-IFNs play common biological functions; they inhibit the pathological cellular effects induced by the virus, induce NK cell cytotoxic functions, and stimulate the expression of histocompatibility complex major molecules (MHC) class I. Besides that, interferons may trigger acute cellular rejection by direct mechanism, based on immune stimulation of alloreactive T cells<sup>20</sup>. Conventional interferon- $\alpha$  and PEG-IFN have distinct pharmacokinetics. Despite the proven higher effectiveness of PEG-IFN compared to conventional interferon- $\alpha$ , there is no confirmed difference in effectiveness between PEG-IFN in chronic hepatitis C treatment.

Although the pulmonary toxicity mechanisms associated with interferons are not entirely clear, it is believed that some of their immunological effects, such as inhibition of suppressor T cells, increase in the cytotoxic T cell action, and induction of pro-inflammatory cytokines are involved in the pathogenesis of pulmonary dysfunctions. On the other hand, it is known that the pulmonary toxicity induced by IFN- $\alpha$  is dose-dependent, intensifies with the length treatment progresses and is reversible upon therapy discontinuation for most patients.<sup>21-23</sup>

### Ribavirin

Ribavirin is a guanosine analog that, in spite of having minimal direct antiviral activity against HCV, shows significant clinical synergism when used in combination with interferon. Thus, ribavirin has reduced direct activity against hepatitis C virus but

acts indirectly based on inosine monophosphate dehydrogenase (IMPDH) inhibition. Paradoxically, high doses of ribavirin reduce lymphocyte proliferation while lower doses increase T-lymphocyte proliferation. During antiviral response, ribavirin acts as a powerful immunostimulatory agent of cytokine production by Th1 lymphocytes (IL-2, IFN- $\gamma$ ) and as an inhibitor of cytokine production by Th2 lymphocytes (IL-4, IL-10). It acts as an inhibitor of the production of tumor necrosis factor alpha (TNF- $\alpha$ ) and IL-1 by macrophages. The predominance of the Th1-type immune response, mediated by the action of cytokines and cytotoxic T-lymphocytes, is essential for eliminating the C virus from the hepatocytes.<sup>20</sup>

Ribavirin's role in the development of pulmonary complications is unknown. There are no reports of severe pulmonary toxicity attributed exclusively to ribavirin and, currently, the recommended treatment for hepatitis C with the interferon-ribavirin combination makes it impossible to investigate its pulmonary toxicity in chronic hepatitis C patients. It is possible, though, that ribavirin may induce pulmonary dysfunctions based on its immunomodulating properties, despite the fact that the reported rates of pulmonary toxicity rates from the IFN- $\alpha$  +ribavirin combination are no higher than those from isolated use of interferon.<sup>24</sup>

## MAIN PULMONARY MANIFESTATIONS DESCRIBED DURING HEPATITIS C TREATMENT WITH INTERSTITIAL LUNG INVOLVEMENT

Interstitial lung involvement, especially Interstitial Pneumonitis and Bronchiolitis Obliterans with Organizing Pneumonia (BOOP), is the main involvement described in that literature that can be attributed to hepatitis C treatment.<sup>25,26</sup> Involvement occurs early, in general in the first few days after the beginning of treatment, and it may occasionally appear later, in up to 30 months after treatment onset.<sup>27,28</sup> These are rare complications with unclear pathophysiologic mechanisms, believed to arise from multi-factorial conditions attributed the changes in alveoli cell membrane resulting from the autoimmune effects induced by IFN- $\alpha$ .<sup>29</sup>

Because such cases are rare, the literature can only refer to case descriptions. Thus, four patients with hepatitis C have been reported<sup>18,19</sup> to have developed interstitial pneumonitis induced by interferon alpha;

three of them developed bilateral pulmonary infiltrates that evolved into acute respiratory failure. Spirometry performed in one patient during the use of IFN- $\alpha$  and two months after its discontinuation showed significant increase in vital capacity (VC) and forced expiratory volume in one second (FEV1) after discontinuation of IFN- $\alpha$ , which suggests that it was a case of restrictive ventilatory disorder associated to the use of IFN- $\alpha$ .<sup>18,19</sup>

Reports of interstitial pneumonitis are also found linked to the use of IFN- $\alpha$  for treatment of other diseases, such as hemangioendothelioma<sup>29</sup> and in hematologic malignancies.<sup>30</sup> The authors called attention to four patients with pulmonary alterations during the use of IFN- $\alpha$  for the treatment of lymphoproliferative and myeloproliferative hematologic diseases; three of them developed interstitial pneumonitis and one had microangiopathy, which initially involved the lungs and then skin and kidneys. Spirometry revealed restrictive-type ventilatory disorder in half of the patients.

The other form of interstitial lung involvement, bronchiolitis obliterans with organizing pneumonia (BOOP), occurred in a patient 60 days after having initiated hepatitis C treatment using IFN- $\alpha$ .<sup>25</sup> Lung biopsy confirmed the clinical suspicion of BOOP. Under spirometry, the patient revealed decreased vital capacity (VC) normal forced expiratory volume in one second (FEV1), which confounded characterization of a specific ventilatory disorder. Total regression of the symptoms after IFN- $\alpha$  discontinuation and use of corticosteroids was also observed.

A more recent study<sup>24</sup> assessed patients with hepatitis C included in four therapeutic clinical trials for the disease. Among them, 54 were treated using PEGylated interferon and 16 were given a combined PEGylated interferon plus ribavirin treatment. Two patients developed interstitial pneumonitis and another two presented with bronchiolitis obliterans with organizing pneumonia (BOOP). Pulmonary function testing was normal in two of the cases: in one patient the results were compatible with restrictive ventilatory disorder, and in the other there was an isolated decrease in CVF. Pulmonary toxicity occurred when interferon alpha was used as monotherapy.

## Sarcoidosis

Pulmonary sarcoidosis is rarely considered a complication related to the treatment of hepatitis C. Three patients with pulmonary sarcoidosis have been

reported<sup>31</sup> in a cohort of 60 patients taking part in a randomized INF- $\alpha$  therapeutic trial with or without associated ribavirin. The authors did not observe any difference in sarcoidosis incidence between groups.

It is possible that the IFN- $\alpha$  may lead to the emergence of pulmonary sarcoidosis by inducing type-Th1 immune response, which is the same immunological pattern found in sarcoidosis. There are no cases of sarcoidosis associated to monotherapy with ribavirin, which reinforces the relevance of IFN- $\alpha$  for that type of toxicity.

### Bronchial hyperreactivity

The bronchial hyperreactivity attributed to hepatitis C treatment was first referred to in 1999.<sup>32</sup> The authors noted severe exacerbation of bronchial asthma in two patients with hepatitis C and mild asthma, between weeks 8-10 after the onset of treatment using IFN- $\alpha$ . A new episode of asthma exacerbation followed a later attempt at reintroducing the discontinued antiviral treatment. There was complete regression of the clinical status, despite the initial severity and rapid emergence of the symptoms, soon after IFN- $\alpha$  was discontinued and corticosteroids were reintroduced. There was no severe asthma exacerbation after the treatment was over, reiterating the role of IFN- $\alpha$  in worsening bronchospasm in those patients.

### Pulmonary Hypertension

Pulmonary toxicity attributed to interferon may also involve pulmonary blood vessels. In 2001, the first case of reversible Arterial Pulmonary Hypertension (APH) during treatment for chronic myeloid leukemia with IFN- $\alpha$  was reported.<sup>33</sup> Stress-induced symptoms dry cough and dyspnea appear in the sixth month of treatment. Doppler echocardiography revealed right heart failure and APH estimated in 80 mmHg. Other causes for APH were carefully dismissed. Regression of the symptoms occurred six months after IFN- $\alpha$  discontinuation, thus characterizing transience of this clinical status.

The pathophysiology of this association is unknown. There is experimental evidence that IFN- $\alpha$  stimulates thromboxane cascade, a possible explanation for the emergence of transient arterial pulmonary hypertension.<sup>34</sup>

More recently, other vascular adverse events attributed to IFN- $\alpha$  have been reported during the use of IFN- $\alpha$  in patients with chronic myeloid leukemia and

melanoma. These include Raynaud's phenomenon with ulceration and digital gangrene, pulmonary vasculitis, pulmonary hypertension and complex thrombotic thrombocytopenic purpura/hemolytic-uremic syndrome.<sup>35</sup> However, concomitant use of hydroxyurea in some patients means that these events may have been caused by this drug alone or in its associated use with IFN- $\alpha$ . Patients had complete resolution of clinical status with the discontinuation of interferon and use of immunosuppressive medicine.

### Pleural Effusion

Pleural effusion was first described in 2000, after IFN- $\alpha$  was used for two weeks in the treatment of chronic hepatitis C<sup>36</sup>. There was a titration increase of antinuclear antibody (ANA) from 1/40 to 1/80, with a homogeneous pattern, with no clinical or laboratory evidence of systemic autoimmune disease. Other eventual causes of pleural effusion were discarded and the clinical status was completely resolved after IFN- $\alpha$  was discontinued.

It is possible that the pleural effusion found in the case reported had been induced by autoimmune phenomena triggered by the IFN- $\alpha$ , as suggested by the ANA increased titration.

### CONCLUSION

We can state that, despite the scarcity of studies available, pulmonary toxicity attributable to IFN- $\alpha$  has been increasingly reported, in practice, among patients using this medication to treat hepatitis C and other diseases. Clinical presentation ranges from asymptomatic status to severe events that may represent risk of death. Nevertheless, there are no controlled or randomized study results available that would include a larger number of patients for thorough investigation on the potentially toxic pulmonary effects of IFN- $\alpha$ .

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