Basic Aspects of the Treatment for Hepatitis C: Mechanisms of Action of Interferon Alpha and Ribavirin and the Bases of Individualization

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Pharmacological Characteristics of Interferons and Ribavirin

The treatment of patients with chronic hepatitis C has developed considerably in recent years. However, it is still based on the use of interferon alpha (IFN-α) as an antiviral and immunomodulatory agent against the hepatitis C virus (HCV).

The IFNs are a family of proteins that are naturally produced by the cells of the immune system. The IFN-á protein presents antiviral, antiproliferative and immunomodulatory activity [1-3]. Its mechanism of biological action occurs through the activation of specific genes, influencing cell growth and division, as well as modulating some immune system activities. Therefore, IFNs have an indirect antiviral effect on HCV [2,4].

Commercially, IFN-α is produced by means of recombinant DNA techniques and is available in preparations of two distinct subtypes (IFN-α 2a or IFN-α 2b), which can be combined with other molecules, such as polyethylene glycolor, more recently, albumin [5,6]. The only difference between IFN-α 2a and IFN-α 2b is in the amino acid present at position 23 of the protein: IFN-α 2a has a lysine at that position, whereas IFN-α 2b has an arginine [7].

After the binding with its specific receptor (IFNAR) on the surface of the target cells, IFN-α activates an intracellular signaling cascade, which takes the induction of IFN-stimulated genes (ISGs), establishing a non-virus-specific antiviral state inside the cell [3,7]. The principal signaling mechanism used by IFN-α is the so-called Janus kinase/signal transducers and activators of transcription (Jak/STAT) pathway [3]. Therefore, two cytoplasmatic proteins with the activity of tyrosine kinase associated with IFNAR, activated Jak1 and tyrosine kinase 2 (Tyk2), are activated by the dimerization of the receptors. Activated Jak1 and Tyk2 perform the phosphorylation of STAT1 and STAT2, respectively. The phosphorylated STAT1 and STAT2 bond with the protein p48 forming IFN-stimulated gene factor 3 (ISGF3), which translocates into the nucleus and bonds with IFN-stimulated regulatory element in the sequences which promote a variety of genes inducible by IFN-α including antiviral proteins such as 2'5'-oligoadenylate synthetase (2'5'OAS), protein kinase RNA, and Mx protein [1,3,7,8].

The absorption of IFN-α (2a or 2b) is high (above 80%) when administrated intramuscularly or subcutaneously. The concentration typically peaks at 3-12 h after administration [9].

The metabolism and elimination of IFN-α occurs principally via the kidneys, with a half-life of 3-8 h [9].

Pharmacological Characteristics of the Pegylated Interferons

Pegylated IFNs (PEG-IFNs) are produced through the binding of an inert molecule of polyethylene glycol to the recombinant IFN-á, thus reducing the renal clearance, altering the metabolism and increasing the half-life of the IFN molecule, although maintaining all of its immunostimulatory characteristics [10,11].

The two PEG-IFNs currently available are produced with polyethylene glycol molecules of different complexities. PEG-IFN-α 2b consists of the binding of IFN-α 2b with a linear PEG chain, forming a 12-kDa molecule. PEG-IFN-α 2a is formed by the binding of two 20-kDa chains with IFN-α 2a, resulting in a complex 40-kDa molecule [6].

The differences in the chemical structure of the two PEG-IFN-α formulations are associated with significant differences in the pharmacological characteristics of the two drugs. The PEG-IFN-α 2b (12 kDa) is more rapidly absorbed (with an absorption half-life of 4.6 h), presents a wide volume of body distribution (approximately 0.99 L/kg) and a mean elimination time of 40 h. However, PEG-IFN-α 2a (40 kDa) is absorbed more slowly (absorption half-life, 50 h), its distribution is restricted to well-vascularized organs with good perfusion, such as the liver, and it remains detectable in the serum for one week (approximately 65 h elimination half-life) [6,12,13].

Pharmacological Characteristics of Ribavirin

Ribavirin is a synthetic nucleoside which is structurally similar to guanosine [14,15]. Ribavirin enters into the eukaryotic cells rapidly and, after it undergoes intracellular phosphorylation, shows virustatic activity against a broad spectrum of DNA and RNA viruses [14,15].

The exact mechanism of the antiviral action of ribavirin has not yet been totally elucidated [1,16]. However, some studies suggest the following possible mechanisms:

a) direct inhibition of HCV replication;
b) inhibition of the enzyme inosine monophosphate dehydrogenase of the host;
c) induction of mutagenesis in the viral RNA;
d) immunomodulation by the induction of a T helper 1 (Th1)-type immune response Ribavirin is rapidly absorbed (half-life of approximately 2 h) and widely distributed throughout the body after its oral administration; its metabolization occurs principally via the kidneys [16].

Treatment with IFN-α has as a success-defining characteristic, progressively more extensive and vigorous immune stimulation. The more rapid the stimulation is, the greater are the chances of success. The study of mononuclear cells ex vivo and in vivo demonstrated that, 3-6 h after the administration of conventional IFN-α, 516 genes were upregulated, of which 88 with actions directly linked to immune functions [17]; the same phenomenon was observed for PEG-IFN, also differentiating responders from nonresponders using the intensity of expression in certain IFN-inducible genes (2'5'OAS, MX1, IRF-7 and TLR-7), greater in the responders and lesser in the Afro-Americans [18,19].

The final pathway of the phenomenon triggered in the cell nucleus is the activation of effector cells. An initial activation of the innate immunity (natural killer cells) is supposedly necessary for the early reduction of the viremia – the greater and the more rapid it is, the more closely it associates with achieving a sustained virological response (also differentiating rapid responders from slow responders). Progressively, as of week 4 of the treatment, the effective immune stimulation induced by IFN with the respective reduction of the viremia would enable the specific defense mechanisms (CD4+ and CD8+ cells) which, in turn, would be in charge of disposing of the residual infected cells (hepatocytes and extrahepatic cells) [20]. In fact, Pillai et al. clearly showed that the magnitude and diversity of the cellular response was associated with early and sustained virological responses [21], in contrast to other authors who only associated the Th1-type cellular response with the initial viremia [22]. At any rate, it is clear that patients presenting a rapid and vigorous initial response have greater chances of success. However, patients presenting a slower response need more long-term stimulation. Therein reside the bases for the individualization of treatment. It is equally clear that this initial virological response depends on the gene stimulus induced by IFN-α. Whether or not these phenomena imply differences associated with the different types of IFNs used in clinical practice has yet to be answered. However, initial evidence was provided by the analysis of the expression of mRNA of inducible IFN genes in two groups of patients exposed to the two existing types of PEG-IFN, suggesting that, despite lower plasma exposure, the patients who used PEG-IFN-α 2b expressed their genes more vigorously, emphasizing the relevance of the intracellular environment in the response to HCV treatment [23].

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