Type I interferon therapies of multiple sclerosis and hepatitis C virus infection

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Abstract

Interferons type I (IFN-I), activated following a bacterial or viral infection, play a major role in the induction and regulation of the immune system. The immune response results in viral RNA and binds to receptors such as RIG-I-like receptors (RLRs) or Toll-like receptors, leading to the IFN-I signaling cascade. Thanks to its cellular function, IFN-I is widely used in therapies for such diseases as multiple sclerosis (MS) and hepatitis C disease (HCD).

MS is a neurological, autoimmune, chronic inflammatory disease of the central nervous system (CNS). During MS, nerve cell demyelination is observed due to the myelin sheaths and oligodendrocyte damage. As a result, neuronal signal and neuron communication are attenuated. The mechanism of MS is still unknown. MS therapy applies interferon- β (IFN- β). IFN- β therapy has been used since the last century, but the therapeutic mechanism of IFN- β has not been completely understood. MS can lead to four syndromes: clinically isolated syndrome (CIS), relapsing-remitting MS (RRMS), primary progressive MS (PPMS), and secondary progressive MS (SPMS).

HCD occurs as a result of infection with the hepatitis C virus (HCV), belonging to the *Flaviviridae* family. HCV is a blood-borne virus with a positive single-stranded RNA. A vaccine for HCV is not available yet. HCD can lead to liver damage or cancer. In HCD interferon- α therapy (IFN- α) is applied. As with MS, the mechanism of IFN- α therapy is not completely known.

Keywords

interferon type I • multiple sclerosis • hepatitis C virus • MAP kinases • NF- κ B • STAT

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Introduction

The body's protection against viral infections is based on the induction and regulation of innate immune mechanisms. An effective immune response leads to the inhibition of cell binding by viruses, their penetration, and nucleocapsid release. New virion formation is blocked due to the disruption of the transcription and translation processes. In consequence, viral mRNAs are degraded, and the synthesis of viral proteins is stopped while the immune system cells are activated to produce antiviral cytokines. Among all the cytokines, interferon (IFN) plays a key role in the regulation of the afore-mentioned cellular processes. The main role of IFN is to provide a very high level of protection against the development of viral diseases by antiviral response activation and anti-proliferative effects, which justifies the use of IFNs as therapeutic agents.

General information about IFN

The IFN is a glycoprotein containing galactose [1] and belonging to the class II helical cytokines. It was discovered in 1957 by Isaacs and Lindenmann, who observed an unknown substance produced by chicken embryo cells during the influenza virus exposition. The name interferon was chosen because this compound interferes with the virus growth and with the spread of the infection to other cells [2].

Based on the nucleotide sequence, IFNs were initially classified into three types: IFN- α , IFN- β and IFN- γ [3]. IFN- α and IFN- β were called leukocyte and fibroblast IFN, respectively, due to their main origin [4], whereas IFN- γ , called immune IFN, is produced by T lymphocytes [5]. Now it is known that the IFNs are produced by most types of nuclear cells. Nowadays, this classification is different and is based on nucleotide sequence homology, interactions with the IFN receptor subunits, gene position on the human chromosome, peptide mapping,

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receptors, and functions in the immune system. IFN- α and IFN- β are a part of the type I IFN family because they are structurally related [6]. Also, IFN- ϵ , - κ , - ω , - δ , - ζ , - τ , and - ν are included in this class. All of them have a similar structure and function. They recognize and bind the interferon type I receptor (IFNAR), containing two peptides: IFNAR1 and IFNAR2. IFN- γ belongs to the type II IFN family and binds a receptor composed of two units: IFNGR1 and IFNGR2. The type III IFN family contains IFN- λ , which binds a receptor consisting of two units: IFNAR1 and IL-10R2 [7].

Type I IFN signaling pathways

The type I IFN can be activated by different signaling cascades: Janus kinases JAK - signal transducer and activator of transcription proteins STAT (JAK-STAT), mitogen activated protein kinase (MAPK) [8], phosphoinositide 3-kinase PI3K-nuclear factor kappa-light-chain-enhancer of activated B cells NF- κ B (PI3K-NF- κ B) or alternative NF- κ B and Crk. The IFN production during viral infection occurs through the activation of signal transduction starting from the cell surface to genes in the nucleus. This pathway is called the JAK/STAT pathway [9], and it is the most common type I IFN cascade. Receptors required for the IFN signal transduction belong to the class II helical cytokine receptors (hCRs). Type I IFNs have a common heterodimeric receptor consisting of low- and high-affinity components, IFNAR1(α) [10] and IFNAR2(β) [11], respectively. The domain IFNAR1 is linked with a tyrosine kinase 2 (Tyk2) [12, 13], and the domain IFNAR2 with Janus kinases 1 (JAK1) [14]. This complex is necessary for the kinase activity, leading to tyrosine phosphorylation [15] and the STAT activation. After the ligand-receptor interaction, the tyrosine phosphorylation of STAT factors takes place [16]. The JAK1 binds to the IFNAR2 and phosphorylates Tyk2, which acquires its enzymatic activity [17]. Activated JAK1 and Tyk2 phosphorylate the IFNAR1, and the STAT2 is bound to the IFN receptor by Src homology region 2 (SH2) domain of STAT2. As a result, these interactions lead to the formation of the STATs homo- or heterodimers and, in consequence, to the activation of STATs dimer. Dimerized STATs are transported to the nucleus, where they become associated with the IFN-regulatory factor 9 (IRF9) to form the ISG factor 3 (ISGF3) transcription factor complex, which binds to the IFN-stimulated response elements (ISRE). As a consequence of the JAK/STAT activation, the transcriptional induction of IFN-stimulated genes (ISGs) is triggered. The ISGs encode direct antiviral effectors or molecules, which positively and negatively regulate the IFN signaling and other host responses. Type I IFN signaling takes place mainly through STAT1 and STAT2 [18], but STAT3 [19], STAT4 [20], STAT5 [21], STAT6 [22] may also be involved in the pathway.

The other signaling cascades, such as the MAPK pathway, NF- κ B, the PI3K pathway dependent on the IKK β activity, the alternative NF- κ B pathway via IKK α , and the v-CRK avian sarcoma virus CT10-homolog-like (CRKL) pathway, may act independently of the JAK-STAT or may cooperate with them.

The type I IFN can activate MAPKs: p38 MAP kinase, c-Jun NH2-terminal kinase (JNK) and extracellular signal-regulated kinase (ERK). After the type I IFN binds to its receptor, JAK1 is activated, which results in tyrosine phosphorylation of the guanine exchange factor (GEF)-Vav [23] by Tyk2 [24]. The Vav phosphorylation leads to the activation of G-proteins such as the Rat sarcoma protein (Ras) and the Ras-related C3 botulinum toxin substrate 1 (Rac1) [25]. Following the activation of Ras, the MAPKK kinase Raf undergoes phosphorylation and, in turn, activates other MAPK kinases MEK1 or MEK2. The phosphorylation of MEK1 and MEK2 leads to the MAP kinases activation, ERK 1 and ERK2, respectively. After the Rac1 activation, TAK1 or MEKK 1 and MEKK 3 undergo phosphorylation. TAK1 activation leads to MKK3 or MKK6 phosphorylation, and as a result, the p38 MAP kinase is activated. Following the phosphorylation of MEKK1 or MEKK3, MKK4 and MKK7 are induced and their phosphorylation leads into JNK activation. Phosphorylated MAP kinases activate different sets of transcription factors. The ERK1/2 causes expression of c-Fos [26], Ets1/2 [27], Elk1, Sap-1 [28], p53 [29], MEF2, STAT1/2, c-Myc, SP1 and SMADs. The p38 activates Fos, ELK1, Sap-1, MEF2, MAPKAP and Rsk. The JNK induces activation of Jun, ELK1, NFAT and ATF2 [30].

Type I IFN receptor stimulation may lead to NF- κ B activation, initiating the phosphoinositide 3-kinase (PI3K) pathway or the NF- κ B inducing kinase (NIK) cascade. The type I IFN and IFNAR interactions lead to receptor activation and tyrosine phosphorylation of IFNAR1. Then, JAK1 and TYK2 are activated, resulting in tyrosine phosphorylation of an adapter protein: the insulin receptor substrate 1 (IRS-1). Next, IRS-1 binds to the SH2 protein, the phosphatidylinositol 3-kinase (PI3K) [31, 32]. STAT3 binds to the IFNAR1 chain of the receptor and plays an adapter role to couple PI3K to the IFNAR1 subunit [33]. Afterwards, PI3K phosphorylates protein kinase B (PKB), also known as Akt [34]. Activated Akt leads to phosphorylation of the I κ B kinase β (IKK β) which results in activation of the NF- κ B [35]. In addition, the activation of Akt kinase stimulates another Akt pathway, where the mammalian target of rapamycin (mTOR) is activated [36]. As a result, proteins engaged in controlling cell division and proliferation, such as glycogen synthase kinase 3 (GSK-3), cyclin dependent kinase inhibitors 1A and 1B (CDKN1A and CDKN1B), are inactivated. NF- κ B can also be activated by type I IFN as a result of I κ B kinase α (IKK α) activity. Moreover, NF- κ B induction is caused by NF- κ B inducing kinase (NIK)

activation mediated by TNF receptor-associated factors (TRAF) phosphorylation [37].

IFN therapy in multiple sclerosis

Multiple sclerosis (MS) is an autoimmune, chronic inflammatory disease of the central nervous system (CNS) of young adults and is more common in women [39]. The disease causes damage to myelin sheaths and oligodendrocytes, resulting in demyelination of nerve cells in white and gray matter of the brain and in the spinal cord neurons. In consequence, MS leads to the neuronal signals impairment and the disruption of the neurons communication [40].

In MS the immune regulation mechanisms are impaired and various cell types become dysfunctional, such as effector and regulatory T cells [40], mainly CD8+ [41], T helper cells CD4+ [42], and also B lymphocytes and plasma cells [43] to a smaller extent. In the course of MS, regulatory T lymphocytes are not able to suppress or downregulate the induction and proliferation of autoreactive effector T cells, which migrate across the blood–brain barrier (BBB) into the brain, by binding to the CNS endothelium. Upon entry to CNS, autoreactive T cells attack myelin sheaths, oligodendrocytes, and axons, which leads to the formation of demyelination lesions. A regulatory defect occurs due to, among other thing, beta-arrestin 1 overexpression in CD4+ T cells [44], which is a positive regulator of the CD4+ T-cell survival and has a critical function in autoimmunity regulation [45].

The MS risk factors are genetics and a family history [46, 47, 48] or environmental factors, such as vitamin D deficiency [49], ultraviolet B light (UVB) [50], Epstein-Barr virus (EBV) infection [51], smoking [52], and obesity [53]. MS is characterized by four syndromes: clinically isolated syndrome (CIS), relapsing-remitting MS (RRMS), primary progressive MS (PPMS), and secondary progressive MS (SPMS). MS symptoms depend on the occurrence of demyelinating plaques. In the case of cerebral damage, the most common manifestations are the following: cognitive impairment, hemi-sensory and motor abnormalities, affective disorder, mainly depression, and, rarely, epilepsy and focal cortical deficits. Demyelination in the cerebellum and the cerebellar pathways results in tremors, clumsiness, and problems with balance. Changes in the brainstem lead to diplopia, oscillopsia, dizziness, speech, and swallowing disorders, which are paroxysmal symptoms. Optic nerve damage in MS patients is reflected in the unilateral painful loss of vision. Due to the spinal cord demyelination, other symptoms are common, such as weakness, stiffness, painful spasms, bladder dysfunction, constipation, and impotence. MS patients can feel pain and fatigue and may have a higher body temperature, sensitivity, and exercise intolerance [54].

In MS therapies, in addition to the most intensively studied IFN- β , various substances like Glatiramer acetate (Copaxone) [55], Mitoxantrone (Novantrone) [56], Natalizumab (Tysabri) [57], and Fingolimod (Gilenya) [58] are used. The IFN- β treatment exhibited advantageous results in *in vitro* and *in vivo* studies and visible positive effects of decreased MS clinical

Figure 1. Type I IFN-activated signaling pathways. The type I IFN can be activated by different signaling cascades: JAK-STAT, MAPK [8], PI3K-NFkB or alternative NFkB. JAK-STAT activation leads to the ISGs induction via tyrosine phosphorylation of the STAT1 and STAT1-STAT2 complex. STATs dimer is transported to the nucleus to create a complex with IRF9 transcription factor and bind to ISRE. NFkB activation may occur via phosphorylation of Akt and IKK β or TRAF and IKK α . Other signaling pathway activates three MAP kinases: p38, JNK, ERK

symptoms were observed. Exact IFN- β mechanisms of action are still unknown because MS pathology is complex and the disease can be caused by many factors. The existing research-based evidence suggests that IFN- β decreases the effects of pro-inflammatory cytokines, increases anti-inflammatory cytokine production, reduces the leukocyte migration across the BBB, inhibits the activation of autoreactive T cells and downregulates T cell resistance to apoptosis.

In MS patients, IFN- α /IFN- β production and secretion are reduced [59, 60], worsening along with the progression of the disease [61]. Therefore, the expression of pro-inflammatory and anti-inflammatory genes regulated by the IFN- β is impaired. During the MS progress, abnormalities in ISG induction have been observed. A reduced level of the ISG products is correlated with defects in the tyrosine phosphorylation level of STAT1. In normal conditions, in the IFN- β pathway, the removal of a phosphate group from STAT1 tyrosine residue is caused by SHP1 phosphatase. In MS patients the SHP1 level is reduced, which results in the increased level of phosphotyrosine-STAT1 [62]. Moreover, a lower level of IFN-responsive factor 1 (IRF1) mRNA was observed in comparison to IRF2 mRNA. A high level of IRF2 mRNA [63] results in the inhibition of expression of several IFN- β -induced gene products. Also, 2'-5'-oligoadenylate synthetase (2',5'-OAS), induced by type I IFNs and dsRNA, is often undetectable during progressing MS [64].

Mechanism of IFN- β action in MS

As mentioned earlier, the mechanism of IFN- β action in MS is not completely understood. IFN- β therapy modifies immune cell responses, which are disturbed by MS. Generally, upon activation, T cells differentiate to T helper (Th1 and Th2 [65]) and T regulatory cells. T helper cells are responsible for the control of various immune response pathways. Type 1 helper T cells (Th1) stimulate cell-mediated responses and produce pro-inflammatory cytokines: IFN- γ (responsible for macrophage activation) [66], LT α (the MS progression marker) [67], and IL-2 (participates in the CD4 T-cell memory) [68]. Type 2 helper T cells (Th2) lead to humoral immune responses and produce anti-inflammatory cytokines such as IL-4, IL-5, IL-9, IL-10, IL-13, IL-25, which activate various effector cells such as eosinophils, basophils, mast cells, and B cells. In MS patients, Th1 cell over-activation is observed in blood, cerebrospinal fluid, and the brain, which is characteristic for the MS disease [69]. Demyelination lesions occur as a result of various pro-inflammatory cytokines, proteases, nitric oxide, and reactive oxygen intermediates secreted by macrophages and T cells that crossed BBB and entered CNS. The progressing MS causes the reduction of Th2 cells, which makes Th2 cell responses ineffective. IFN- β treatment

inactivates Th1 cells. Regulatory T cells are activated by anti-inflammatory cytokines secreted by increased amount of Th2 cells. T-cell analyses in MS patients after IFN- β therapy show occurrence of a Th1 to Th2 shift [70]. Another mechanism of IFN- β action in MS is downregulation of the B cell stimulatory capacity. IFN- β treatment decreases the CD40 expression of B cells of MS patients. Likewise, in MS patients the inhibition of CD80 expression by IFN- β was also observed.

IFN- β promotes apoptosis of mature dendritic cells (DC) by activation of NF- κ B and STAT1. These transcription factors lead to caspase-11 and caspase-3 activation. Mature DC cell death occurs when NF- κ B activation is induced by the inflammatory cytokines or upon activation of the MyD88 signaling pathway, the TLR ligands. Also, mature DC apoptosis is activated by STAT1 upon IFN receptors signaling [71]. Due to the fact that DCs take part in T cell migration into CNS [72], they are sufficient to induce the autoimmunity in CNS [73], and an increased number of DCs is observed in murine experimental autoimmune encephalomyelitis (EAE) [74]. The pathogenic role of DCs in MS is the secretion of pro-inflammatory and anti-inflammatory cytokines, which activate interleukin 17 producing T helper cells (Th17 cells) [75]. Th17 cell development is induced by IL-23 and IL-1 β [76]. In MS patients, high numbers of Th17 cells are observed [77], resulting in a higher production of pro-inflammatory cytokines: IL-17 [78], IL-6, IFN- γ [79]. Furthermore, in IL-17 deficient mice EAE had a delayed onset, histological changes were improved, and earlier recovery was observed [80], suggesting a significant role of Th17 cells in MS. In DCs, IFN- β reduces production of pro-inflammatory cytokines (IL-23 and IL-1 β) and leads to increased production of the anti-inflammatory cytokine IL-10 [81], which suppresses Th17 cell activity [82]. IFN- β decreases DC capacity to IL-17 production by the CD4 T cells and activates IL-27 expression by DC, which also has been confirmed in a mouse EAE model [81]. Other studies of the role of IFN- β in MS show the inhibition of the expression of C-C chemokine receptor type 7 (CCR7) and induction of matrix metalloproteinase 9 (MMP-9) production in mature DCs mediated through STAT1. As a result, the ability of DCs to migrate from the inflammatory site to a draining lymph node is reduced [83].

As mentioned earlier, the BBB has an essential role in MS, because disease occurrence is due to T-cell migration across the BBB, followed by the creation of demyelination lesions [84]. The BBB regulates migration of immune cells from the periphery to CNS through tight junctions formed by endothelial cells. The T cell entrance into CNS is caused by abnormal BBB permeability, resulting from the decreased expression of proteins involved in the creation of tight junctions between endothelial cells, occludin [85], claudin-3 [86], VE-cadherin, vinculin, and N-cadherin [87]. In MS patients, the secretion of IFN- γ reduces the expression of the tight junction proteins.

IFN- β therapy inhibits the IFN- γ activity, leading to enhanced expression of the tight junction proteins. As a result, IFN- β at least temporarily decreases the BBB permeability in RRMS patients [88].

IFN- β treatments

In 1981 IFN- β was first used in MS [89], and in 1993 the treatment was approved as a disease-modifying therapy (DMT) by the US Food and Drug Administration (FDA). In this first therapy, RRMS patients were selected who were on the extended disability status scale (EDSS) and had experienced at least two attacks in the prior two years. They were divided randomly into the placebo group, the IFN- β -1b low-dosage group (1.6 MIU; 50 μ g), and the IFN- β -1b high-dosage group (8 MIU; 250 μ g). IFN- β -1b (Betaseron; Berlex Laboratories, Montville, NJ) was injected subcutaneously every other day for two years. As a result of the two-year treatment, the IFN- β -1b high-dosage group had a reduced clinical relapse rate ($\sim 34\%$; $p < 0.0001$) and lower attack rate, compared with the placebo [90, 91, 92].

In 1996, IFN- β -1a (Avonex; Biogen, Cambridge, MA) was administered intramuscularly to MS patients once per week for two years. The patients with RRMS had an EDSS score of 1.0–3.5 and had experienced at least two attacks in the three years prior to entering the study. They were divided into two groups: placebo-treated patients and IFN- β -1a-treated patients (6 MIU, 30 μ g). The trial was stopped earlier, and only 57% of the patients received the treatment for two years. As a result of this trial, it was observed that patients receiving IFN- β -1a had a reduction in EDSS progression rate. Also, the attack rate was improved after two years in the IFN- β -1a-treated patients, compared with that of the placebo [93, 94, 95, 96, 97].

Six years later, RRMS patients were selected in another trial with an EDSS score ≤ 5.0 and at least two attacks in three years before starting the trial. For two years, three times per week, three groups of patients were treated with placebo, 6 MIU (22 μ g) of IFN- β -1a, or 12 MIU (44 μ g) of IFN- β -1a (Rebif; Serono International SA, Geneva, Switzerland), respectively. After this trial, IFN- β -1a was shown to reduce the EDSS progression rate and improve the attack rate [98, 99].

All these drug therapies were randomized, separately tested in the double-masked and placebo-controlled clinical trials.

Side effects of IFN therapy in MS patients

The IFN- β therapy can be associated with a number of side effects [100]. The most common are flu-like symptoms. Three

to six hours after the IFN- β injection, MS patients may have a fever, muscle pains, and headaches and may feel chills and fatigue. The flu-like symptoms decrease after 24 hours. The symptoms appear due to the secretion of IL-1, tumor necrosis factor (TNF), and IL-6 [101]. Along with the flu-like symptoms, 3 to 24 hours after the IFN- β injection, additional symptoms may appear, such as enhanced spasticity [38] and functional deterioration such as a deterioration of visual acuity or paresthesia. The IFN- β -treated patients can have these symptoms for several hours to several days. Another frequent symptom in MS patients during the IFN- β therapy is depression, manifested by passiveness, insomnia, appetite lack, pessimistic hopelessness, and lack of interest [100, 102]. Using IFN- β is also limited by the pain associated with injections and inflammation at injection sites. The injection site complications depend on the IFN- β administration route. The intramuscular injection has less influence on the skin condition, and the pain is decreased in comparison with the subcutaneous injection. IFN- β administered subcutaneously caused hardened, irritated, and locally painful skin in MS patients, and in some patients skin necrosis was observed. Likewise, MS patients have abnormalities in blood laboratory tests. The most common irregularities are leukopenia, lymphopenia, neutropenia, and elevated values of liver aminotransferases. Studies and clinical trials have shown more side effects during IFN- β therapy, such as menstrual disorders, hearing loss, alopecia, anaphylactic shock, and psoriasis, but some of them are very rare [100].

IFN therapy in hepatitis C virus infection and hepatitis C disease

Hepatitis C virus (HCV) infection may lead to an acute or a chronic hepatitis C disease (HCD). HCD can be a mild illness that lasts several weeks, or it can be a serious, lifelong disease. The consequences of chronic infection include cirrhosis, liver cancer, or other liver diseases, and almost 400,000 patients with chronic HCD die each year. According to the 2018 report from the WHO, 71 million people have chronic HCD. Ninety-five percent of the people infected with HCV may be cured by antiviral drugs, but in many countries diagnosis and treatment are still at a very low level. Currently, the HCV vaccine is not available [103]. HCV is a bloodborne virus that is sexually transmitted or can be passed from mother to child or via used or unsterile injection equipment such as syringes and needles, as well as HCV-infected blood transfusion [104]. HCV was discovered in 1978 [105] but isolated in 1989 and called bloodborne non-A, non-B hepatitis virus [106]. HCV is a positive single-stranded RNA virus, belonging to the *Flaviviridae* family and genus *Hepacivirus*. HCV contains a lipid envelope to which structural proteins are attached,

glycoproteins E1 and E2, responsible for HCV entering into cells. Also, HCV has a capsid protein and nonstructural proteins p7, NS2, NS3, NS4A, NS4B, NS5A, and NS5B, which catalyze HCV replication [107].

Mechanism of IFN action in HCV infection

Type I IFN plays an essential role in the immune defense against viruses. During the HCV infection and replicon replication, the reduction of ISG expression is observed, hence the antiviral response is suppressed [108]. IFN- α administration to HCV-infected patients activates ISG expression [109], causing a decreased, almost undetectable, HCV level. IFN- α inhibits HCV replication via several mechanisms, but they are not very well known or understood yet. Studies have demonstrated that IFN- α presence leads to decreased stability of amplified positive-strand RNA and a twofold reduction of the directed translation of HCV internal ribosomal entry site (IRES). Interestingly, IFN- α has no direct impact on viral RNA synthesis. IFN- α inhibits various steps of the HCV replication cycle, and viral protein translation and RNA amplification are consequently suppressed [110]. Subsequent studies show that during IFN- α therapy, HCV replication is restricted via a mechanism involving the PKR and P56 pathways. The PKR pathway is controlled by the NS5A sequence, and it has an influence on HCV RNA translation efficiency. Likewise, the P56 pathway, induced by IFN- α , is involved in disturbing the viral IRES function, which results in the suppression of HCV RNA replication independently of the PKR pathway [111].

IFN- α treatments

For almost 30 years, patients with HCD have been subjected to IFN- α treatment. During this therapy, a polyethylene glycol (PEG)-ylated IFN- α (PEG-IFN) is administered subcutaneously in combination with orally administered antiviral agent e.g. ribavirin. This therapeutical strategy leads to a prolonged antiviral response (SVR) and lead to HCV RNA elimination from blood in 24 weeks after treatment. Unfortunately, this therapy leads to many side effects, and for patients with advanced chronic disease the treatment is less effective and poorly tolerated.

Initially, IFN- α -2b (Introna) was used in only therapy. HCD patients participated in an open, prospective, randomized, and controlled trial, where they were divided into two groups, IFN- α treatment and control groups. IFN- α (3 MU) was given subcutaneously to treat patients three times weekly for 36 weeks. As a result, in almost half of the IFN- α -treated patients, a highly significant normalization of aminotransferases was observed, but in the control group, some patients had a

similar response. IFN- α -treated patients had improvement of their liver inflammation, which was not observed in the control patient group. Only in around 30% of patients did IFN- α therapy lead to SVR, which was disappointing [112].

To improve the SVR, IFN- α therapy can be enhanced with ribavirin, which is a nucleoside analogue that has a wide activity spectrum against DNA and RNA viruses. In a pilot study, IFN- α and ribavirin combination was given to patients. Initially, a group of 20 HCD patients were treated three times a week with IFN- α (Alfaferone; Alfa-Wassermann, 3 MU) for six months. In this group, 10 patients had a transient IFN- α treatment response with relapse (RR), and 10 patients had no response (NR). Subsequently, the NR group was treated with the IFN- α and ribavirin combination, and the RR group received only IFN- α . As a result, the IFN- α without ribavirin retreatment did not lead to the sustained inhibition of HCV viremia, but transient viremia suppression and some normalization of aminotransferases levels were observed. The combination of IFN- α and ribavirin treatment was able to induce SVR and the sustained normalization of aminotransferases levels [113].

Another method of therapy improvement is a covalent attachment of PEG to IFN- α , which overcomes or reduces several limitations of IFN- α therapy, such as short half-life, necessity of frequent injections, and side effects. PEG is a polymer that is nontoxic and soluble in water and that can be attached to a protein. PEG attachment to IFN- α modifies its properties by extending its half-life, reducing immunogenicity, and improving its biologic activity [114].

A group of HCD patients participated in an open, randomized, and active controlled IFN- α (Intron) trial. They were divided into eight treatment groups and received different amounts of PEG-IFN- α (0.35, 0.7, and 1.4 mg/kg) with various doses of ribavirin (600, 800, 1,000, and 1,200 mg/day). As a result, PEG-IFN- α antiviral effect was increased due to the addition of ribavirin. Furthermore, the combination of PEG-IFN- α and ribavirin was well tolerated and safe for patients, promising long-awaited progress in the treatment of HCD. Many studies and trials were performed using IFN- α -PEG with ribavirin that showed SVR and a significant improvement in the normalization of aminotransferases levels in HCV-infected and HCD patients [115].

Side effects of IFN therapy in HCD patients

Initially, the side effects of IFN therapy in HCD patients were classified as mild and tolerable. After several IFN- α injections, patients had brief flu-like symptoms. After some time, fatigue, myalgia, and apathy were reduced [112]. However, years of IFN- α therapy studies have shown that treatment of HCV and HCD may lead to more complicated long-term side effects and complications. One of the major side effects is

retinopathy, manifested by flame-shaped hemorrhages and cotton wool spots at the bottom of the eye. Additionally, in some patients after several IFN- α treatments the loss of vision was observed [116]. Moreover, frequent and persistent side effects of IFN- α therapy are depression, cognitive impairment, insomnia, nausea, alopecia, and dermatitis [117, 118]. Also, IFN- α treatment may lead to type 1 diabetes mellitus (T1D), which may develop a few months after the first IFN- α injection. However, patients who terminate therapy are also at risk of developing T1D disease [119].

Authors' Contributions

I.J.: Designing the figures, drafting the article or revising it critically for important intellectual content, writing the manuscript, literature review, final proofreading and approval of the version for publication; J.S.: Supervising the project, drafting the article or revising it critically for important intellectual content, writing the manuscript, literature review, final proofreading, and approval of the version for publication

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Conflict of Interest

The authors have no potential conflicts of interest to declare.

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