

HISTORY OF INTERFERON TREATMENTS IN MULTIPLE SCLEROSIS – 60 YEARS OF PROGRESS

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Abstract

Interferons are biopharmaceutical agents which were discovered based on the phenomenon of viral interference, in 1957. Three categories of interferons were described: IFN I (IFN- α , IFN- β), IFN II (IFN- γ) and IFN III (IFN- λ). These cytokines, whose importance is comparable to that of penicillin, act on specific receptors and activate the signal transducer and activator of transcription (STAT) complexes which regulate the expression of over 200 genes of the immune system. Based on their antiviral and immunomodulatory effects, they were approved in 1993 for the treatment of multiple sclerosis, becoming a part of the Disease Modifying Therapies - DMTs drugs category. The studies that followed demonstrated a long term good safety profile and an acceptable efficacy. New formulas meant to improve the adherence to treatment, were approved recently. At the moment, the research is focused on developing new pharmacogenetic markers for enabling a personalized treatment with IFN. This treatment should approach to the score of 4 points in NEDA (no relapses, no disability progression, no MRI activity, and no change in the brain volume).

Rezumat

Interferonii sunt agenți biofarmaceutici ce au fost descoperiți pornind de la fenomenul de interferență virală, în 1957. Au fost descrise trei mari categorii de interferoni: IFN I (IFN- α , IFN- β), IFN II (IFN- γ) și IFN III (IFN- λ). Aceste citokine, a căror importanță este comparabilă cu cea a penicilinei, acționează pe receptori specifici și activează complexele *signal transducer and activator of transcription* (STAT) care reglează expresia a peste 200 de gene ale sistemului imunitar. Considerând efectele lor antivirale și imunomodulatorii, în 1993 au fost aprobați pentru tratamentul sclerozei multiple, intrând în categoria medicamentelor care modifică evoluția bolii (*Disease Modifying Therapies* - DMTs). Studiile care au urmat, au demonstrat un bun profil de siguranță pe termen lung și o eficacitate acceptabilă. Noi formule care să îmbunătățească aderența la tratament au fost aprobate recent. În momentul de față se caută *markeri* farmacogenetici pentru implementarea tratamentelor personalizate cu IFN, care să se apropie de scorul 4 NEDA (fără pusee, fără progresia invalidității, fără semne de activitate imagistică și fără modificări ale volumului creierului).

Keywords: interferon, cytokine, personalized medicine, biological therapy

Introduction

Interferons (IFNs), biopharmaceutical agents, are signalling proteins, which belong to the class of cytokines, produced and released by cells, in the presence of pathogens such as: viruses, bacteria, parasites or tumour cells. Their name derives from their ability to interfere with viral replication and, in this way, to protect the infected cells, acting through complex mechanisms involving the immune response activation [13].

Immunomodulatory properties of IFNs have been demonstrated in numerous studies. Thus, in the few decades since their discovery, interferons were assigned important roles in the infectious, neoplastic, inflammatory, autoimmune or metabolic processes,

today being used for the therapy of chronic viral infections, malignancies, multiple sclerosis and other inflammatory pathologies. IFNs systemic use in high doses and for long periods of time, as they are currently administrated, it is still difficult to accept by the body [3, 24].

There are several types of IFN, according to signalling receptors:

- Type I IFNs that link to type α or β receptors [14]. They are produced by monocytes and fibroblasts and prevent the replication of viral RNA and DNA. IFN- α is used in the treatment of B and C virus - hepatitis and IFN- β is used to treat multiple sclerosis.
- Type II IFN, human IFN- γ , is activated by interleukin-12 and released by T-helper-1 cells, inhibiting

the proliferation of T-helper-2 cells. The two cell types Th1 and Th2 activate different ways of immune response. In this way, IFN- γ worsens multiple sclerosis [14, 30].

- Type III IFN, IFN- λ is the most recently discovered, and the cellular signaling implies complex receptors IL10R2 (CRF2-4) and IFNLR1 (CRF2-12). It plays an important role in some viral infections, being similar, from this point of view, to IFN I α or β [23].

IFNs act on their specific receptors and activate the signal transducer and activator of transcription (STAT) complexes which regulate the expression of over 200 genes of the immune system [1, 41]. IFN type I (IFN- α and IFN- β) use a common complex receptor IFNAR, whose genes are located on 21 human chromosome [46]. Even if they have the same receptors, IFNs α and β cause different biological effects. IFN- γ links to the IFNGR receptor, and IFN type III links to IFNLR1 and IL10R2 receptors.

Brief history of the discovery of interferons

At the basis of the discovery of IFNs, it was the phenomenon of viral interference, explained by the inhibition of virus replication. This means that, under certain conditions, the animal cells infected with a virus cannot develop a second one. Viral interference was first highlighted in 1804 by the physician Edward Jenner who noticed that herpes infections hampered the vaccine virus to act, and it was named by the British researchers Gerald Frank Findlay and MacCallum in 1937 [19].

Yasuichi Nagano and Yasuhiko Kojima, Japanese researchers from the Institute for Infectious Diseases of the University of Tokyo, Japan, have discovered an "inhibitor viral factor", while they were trying to get a better vaccine against smallpox, using rabbits, publishing their discovery in 1954 [38].

However, the discovery of interferon is attributed to the British virologist Alick Isaacs and the Swiss researcher Jean Lindenmann, from the National Institute for Medical Research in London, UK, who called this inhibitor factor "interferon" in 1957 [26, 27, 33].

However, Polish-born American doctor, Sidney Pestka is known as the "interferon's father". In the laboratories from the Roche Institute of New Jersey, USA, he tried to purify interferon obtained from rabbits and he discovered the two types of interferons alpha and beta. These concerns were also specific to other laboratories in the world [24]. The amounts of IFN produced in the body are infinitely small, but it is a highly potent molecule. As a result, the main problem was obtaining the purified form of interferon and in sufficient quantities for research and therapeutic purposes.

In 1960, Kari Cantell from the National Blood Transfusion Service from Helsinki, Finland, has developed a synthesis pathway for interferon with a purity of only 0.1% on human lymphocytes, implying the exposure to increased Sendai virus on chicken embryos [9, 43].

In 1962 it was conducted the first clinical trial on human volunteers, which demonstrated that IFN was devoid of side effects, but refuted by subsequent research work [42].

An analysis of 25 studies, made by Finter in 1966, concluded that not only the dose and site of administration of interferon is important, but also the time of administration, in connection to the onset of viral infection. The study also showed the difficulty to obtain sufficient quantities and optimal purity of IFN [4].

In 1967, Friedman found that IFN links to the specific receptors at the cell's surface [17].70s were the golden age of IFNs, considered to be able to cure all diseases, but especially neoplasia [43].

Ion Gresser and collaborators have demonstrated that the *in vivo* inactivation of IFN by administering neutralizing agents, dramatically influence the evolution of infections in various animal species [22].

The attempt to obtain IFNs from fibroblasts and leukocytes, in several laboratories in the world, led to another discovery namely that these molecules are different. In this way there were discovered the IFN- α (the main component of leukocyte IFN) and IFN- β (the main component of fibroblast IFN) interferons [12].

Branca and collaborators published in 1981 evidence that the type I IFNs have a common receptor, different from the type II IFNs receptor [5]. The multigenic nature of genome encoding in the IFN became evident in the same year [21]. In the search for solutions to obtain greater amounts of IFNs, the 1980s represented a huge step forward, enabling the cloning and expression of a gene for human IFN- α in *Escherichia coli* and later for human IFN- β , leading to products that have a comparable activity to the natural IFNs [15, 39].

The systemic side effects of IFNs are: malaise, low grade fever, chills, myalgia, fatigue, leucopenia, hepatic cytolysis, depression, and hypothyroidism. They are explained by the state of cellular stress, caused by the release of inflammatory cytokines (IL-1, IL-6, TNF- α), due to the systemic administration of large amounts of IFNs for long periods of time. The mean discontinuation rates due to side effects ranged from 16% to 27% [10]. They appear at the initiation of the treatment and disappear after a period of time [18]. For this reason, the PEGylation of interferon is an important step, because the half-time increases, the doses administered in this case being smaller. Beside the systemic effects, there are

also local effects, represented by erythema, pain, pruritus, trophic changes.

The immunogenicity of biopharmaceuticals such as IFNs may represent an obstacle in the treatment's efficacy, by the appearance of antidrug antibodies (ADAs), affecting pharmacokinetics, bioavailability and autoimmunity [45].

The history of IFNs therapy in multiple sclerosis

Multiple sclerosis (MS) is a neurodegenerative disease that affects mostly young adults, with an evolution of over 30 years, which affects the quality of life and reduces life expectancy by about 6 - 7 years [32].

It is possible that the first case ever described belongs to a Dutch woman, Saint Ludwina of Schiedam (1380 - 1433) as we learn from the archives from Vatican, where there are documents on the signs, symptoms and the evolution of the disease. At sixteen she fell on ice, giving evidence of weakness in the limbs. She recovered for a while, then began to exhibit outburst imbalances, abnormal vision, muscle weakness initially remitted. The disease progressed and escalated, and eventually led to premature death at the age of 53 years [29]. We thus indirectly have an estimation of the natural evolution of the disease, the evolution uninfluenced by therapeutic interventions, 37 years, which corresponds to the subsequent data obtained from different researches.

In the nineteenth century, an empirical treatment of the disease was established, sometimes with a relative toxic or lethal potential: different plants, animal products, organic solvents such as chloroform, hydro and electrotherapy, exercise, diet, etc., but of course without tremendous beneficial results [36].

Since the 1960s, therapies for MS have been directed towards two pathogenic pathways valid nowadays: autoimmune attack on myelin and existing antiviral antibodies of the MS patient. It was also speculated the viral hypothesis for causing this disease [25].

In 1969 it was conducted the first controlled clinical trial that demonstrated the adrenocorticotrophic hormone (ACTH) effects, administered intramuscularly, in the efficient recovery of patients after relapse. There were used the standardized diagnostic criteria and the evaluation scales developed by experts [37]. It was the first time the disease had a beneficial treatment, demonstrated on a scientifically elaborated base. Thus, corticosteroids have remained until today the elective treatment in the acute phase of the disease, proving once again the role of inflammation.

In 1979 a group of neurologists with expertise in MS have published guidelines for conducting clinical trials in multiple sclerosis [6]. IFNs were

investigated for their potential curative role in MS, starting from their properties demonstrated on animal models: antiviral, immunomodulatory, anti-tumour. Due to biotechnology, they could obtain the required quantities of INFs beta 1-a and 1-b, recombinant, in *E. coli* and other microorganisms. The results were positive, proving the INFs' effectiveness as immunomodulatory agents useful in treating MS.

The IFN- β therapy started through pilot studies conducted in United States, published in 1993, studies that demonstrated their effectiveness in the relapsing - remitting MS (RRMS) forms [34, 40]. Thus, nearly four decades after the discovery, interferons have proven to be effective in multiple sclerosis.

It has been shown that they reduce the frequency of relapses, delaying the appearance of disability, and along with glatiramer acetate copolymer, entered the class of the disease - modifying therapies (DMTs). So, they are considered the first choice medication in the background therapy of the disease, in relapsing - remitting forms [28, 44]. In 1998, IFN β -1b has proven effective also for the secondary progressive forms of the disease (SPMS) [16].

The mechanism of action of IFN-beta in MS is not fully elucidated. It is considered to increase the production of anti-inflammatory cytokines, inhibiting pro-inflammatory ones, preventing trafficking of immune cells in the blood - brain barrier and stimulating the production of growth factors [1]. Studies with alpha and gamma IFNs haven't had the expected results, so they were abandoned in MS therapy.

Studies concerning IFN β -1a, ETOMS (Early Treatment of Multiple Sclerosis) and CHAMPS (Controlled High-Risk Avonex Multiple Sclerosis), published in 2001, respectively 2002, have proven the efficiency and importance of an early treatment in MS, with a delay conversion of CIS (clinically isolated syndrome) forms in clinically defined MS. Also, the studies with IFN- β , INCOMIN (Independent Comparison of Interferons) and EVIDENCE (Evidence of Interferon Dose - response: European North American Comparative Efficacy), published in 2002 and respectively 2007, revealed the importance of frequent and high doses administration in RRMS [34].

The six biopharmaceutical products, approved by the Food and Drug Administration for the first intention treatment of RR forms of multiple sclerosis, that are based on IFN- β , are: IFN- β -1a (Avonex[®] - 2002, Rebif[®] - 2009), obtained by glycosylation of interferon beta-1b in hamster ovary cells; IFN- β -1b (Betaseron[®] - 1993 and subsequently Betaferon[®] for Europe), non-glycosylated forms derived from *Escherichia coli*; IFN- β -1b

biosimilar (Extavia[®] - 1993); Peginterferon beta-1a (Plegridy[®] - 2014) – (polyethylene glycol) PEGylated interferon beta-1a.

Approximately 45% of the patients develop neutralizing antibodies against IFN- β in the first 3 - 18 months of treatment. IFN- β 1b is more immunogenic than IFN- β 1a. When it is administered subcutaneously (Rebif[®]) it more likely to develop antidrug antibodies (ADAs) than administered intramuscularly (Avonex[®]) [33]. The role of neutralizing antibodies cannot be assessed with certainty for numerous reasons: unpredictable evolution of the disease, low efficiency of treatment with IFNs, different immunogenicity of pharmaceutical preparations.

All interferons used to treat multiple sclerosis have the disadvantage that they have to be injected with a high frequency, which varies depending on the preparation, reducing patient adherence to treatment because of the caused discomfort [7].

It is also the reason why peginterferon beta-1a was approved in 2014. It was obtained by conjugation of IFN- β with polyethylene glycol (PEG), following the pattern of other drugs, which have improved stability, solubility, half-life, and efficacy. Peginterferon beta-1a has an improved pharmacokinetic and pharmacodynamic profile and fewer side effects compared to the classic form [2]. Current therapies with interferons decrease the number of flares with 1/3, reduce the number of lesions detected by imagistic procedures with 70% and delay disability progression.

Developing medicines for the treatment of MS have as target the “no evidence of disease activity” (NEDA) criteria, score 4 being a target for the intended purpose (no relapses, no disability progression, no MRI activity, and no change in brain volume) [20]. To this aim, personalized medicine is of great interest. Identifying responders to the treatment with IFN- β is a laborious process, the pharmaco-genomic markers not being found, so far, in order to establish the efficiency criteria of the treatment [11, 36].

Conclusions

After 60 years since the discovery of interferons and after 23 years of use in the relapsing-remitting and secondary progressive forms of multiple sclerosis, IFN- β remain the first-line chronic treatment for eligible patients. They have a good benefit-risk ratio, proven on a large number of patients in randomized trials. However, the medicine of the future, aims finding specific pharmacogenomic markers that indicate which patients will respond best to the individualized treatment, to approach as much as possible to the 4 NEDA score.

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