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Review

REVIEW

Beta interferons as immunotherapy in multiple sclerosis: a new outlook on a classic drug during the COVID-19 pandemic

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Summary

Beta interferons (IFN-β) are pleiotropic cytokines with antiviral properties. They play important roles in the pathogenesis of multiple sclerosis (MS), an incurable immune-mediated disorder of the central nervous system. The clinical expression of MS is heterogeneous, with relapses of neuroinflammation and with disability accrual in considerable part unrelated to the attacks. The injectable recombinant IFN-β preparations are the first approved disease-modifying treatments for MS. They have moderate efficacy in reducing the frequency of relapses, but good long-term cost-efficacy and safety profiles, so are still widely used. They have some tolerability and adherence issues, partly mitigated in recent years by the introduction of a PEGylated formulation and use of 'smart' autoinjector devices. Their general impact on long-term disability is modest but could be further improved by developing accurate tools for identifying the patient profile of best responders to IFN-β. Here, we present the IFN-β-based immunomodulatory therapeutic approaches in MS, highlighting their place in the current coronavirus disease (COVID-19) pandemic. The potential role of IFN-β in the treatment of COVID-19 is also briefly discussed.

Introduction

Endogenous interferons (IFN) are multimodal pleiotropic signaling proteins of the cytokine class and key components of the innate immune system.[1] They were first described for their ability to interfere with viral replication,[2] but they have a broad spectrum of immunomodulatory, antiproliferative and tissue-specific functions.[1,3] Based on their biologic characteristics, they are classified in type I [including IFN-α, beta interferons (IFN-β) and others], type II (a single IFN-γ species) and type III (IFN-λ).[1,4]

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IFN-β are produced by virtually all cells in the human body, even in the absence of infection.[5] The downstream effects of IFN-β depend on the complex interplay between the trigger and the magnitude of the IFN-β response (or the exogenous/recombinant pharmacological IFN-β product), and the local environment and the peculiarities of the type I IFN receptor (IFNAR) and IFN regulated genes and pathways.[4,5] In high concentrations, such as in the case of acute viral infections or when administered pharmacologically, IFN-β have net anti-inflammatory effects, increasing the expression of anti-inflammatory cytokines and decreasing the pro-inflammatory ones.[6]

Most immune-mediated diseases, in particular those mediated by autoantibodies, are exacerbated by IFN-β and the peripheral blood mononuclear cells (PBMCs) of people with these diseases show increased expression of type I IFN regulated genes (or IFN signature).[1] Contrarily, the PBMCs of most untreated people with multiple sclerosis (MS) show a decreased type I IFN signature,[5,7] finding also supported by our studies.[8] IFN-α also seems beneficial in MS, but to a lesser extent and has not been broadly used for this indication.[7,9]

The new coronavirus disease (COVID-19) pandemic has brought IFN-β in the limelight as a potential therapy. Here, we present the current IFN-β-based therapeutic approaches in MS, briefly summarizing the commercially available pharmacological products, with emphasis on data relevant for a broader audience of clinical practitioners. We also highlight their place in the MS therapeutic armamentarium in the context of the COVID-19 pandemic and briefly discuss their potential role in the treatment of COVID-19.

IFN-β as disease-modifying treatments for MS

MS is an incurable immune-mediated disease of the central nervous system (CNS).[9,10] It affects up to 2.5 million people worldwide and has high socio-economic burden.[10] MS is a disease with a multifactorial pathogenesis. This involves the interaction between environmental and lifestyle factors [such as chronic viral infections, especially with Epstein–Barr virus (EBV), but also cytomegalovirus and others,[11] vitamin D deficiency,[12] smoking[13] and obesity,[14] the western lifestyle with impact on the microbiome and the loss of evolutionary microbes and gut parasites[15]] with the individual's genetic factors, including the expression of endogenous retroviruses[16] and the polymorphisms of the IFN, IFNAR and IFN regulated genes.[4,5]

The typical clinical onset of MS is in young adulthood, with diverse presentations, depending on the sites of the lesions.[10] In most cases, the clinical course is with relapses/attacks of CNS inflammation followed by partial or complete remissions—i.e. relapsing-remitting MS (RRMS).[10,17] Over the years, most people with RRMS enter a secondary progressive phase [secondary progressive MS (SPMS)], characterized by steady disability accrual, with or without relapses.[10,17] A minority of the people with MS have a progressive course from the beginning, sometimes with superimposed relapses—i.e. primary progressive MS (PPMS).[10,17]

Irrespective of its clinical phenotype, MS pathology comprises mainly of focal white and gray matter inflammatory demyelinating lesions with dissemination in space and time, diffuse widespread CNS inflammation, axonal injury and neurodegeneration.[10] This is in close relation with the two main axes on which MS develops: disease activity, assessed using the number of clinical relapses and number of new or active white matter lesions, and disease progression, estimated based on the steady disability accrual in substantial part unrelated to relapses and on CNS atrophy.[10]

The disease-modifying therapies (DMT) currently approved in MS address the inflammatory component of the disease, being either immunomodulators or immunosuppressants.[18–20] DMT are expensive but cost-effective and thus reimbursed by most healthcare systems.[9,21,22] Recombinant IFN-β were the first DMT approved for MS.[9] They are still widely used because of their good long-term cost-effectiveness and safety.[21,22] They have moderate effectiveness in relapsing MS (i.e. RRMS and SPMS with relapses), decreasing the annualized relapse rate (ARR) by around a third.[20,23] Several high efficacy drugs, that reduce the ARR by around 70%, have also been developed and approved over the past decade, but these pose greater safety concerns.[20] More recently, the monoclonal antibody ocrelizumab, and the sphingosine-1-phosphate receptor modulator siponimod, have been approved for the treatment of progressive forms of MS (PPMS and SPMS, respectively). The overall impact of all available DMT on long-term disability and quality of life is variable, and longer term follow-up is needed to assess if this impact is beyond modest at best.[18–20]

The mechanism of action of pharmacological IFN-β is mainly immunomodulatory, but it is incompletely understood. Putative pathways include increased production of regulatory T cells, a Th2 cytokine shift, reduced activation of T cells and depletion of memory B cells (the reservoir of EBV).[6,11,19,24] Besides these main mechanisms, IFN-β-based drugs may also interfere with the replication of EBV and other viruses, as well as with the expression of human endogenous retroviruses, which are likely involved in the pathogenesis of MS.[11,16] Additionally, IFN-β may decrease the permeability of the blood–brain barrier (BBB), lower the number of lymphocytes that enter the CNS, promote neuroplasticity and neuroregeneration, protect the oligodendrocytes (i.e. the glial cells that produce and maintain the myelin stealth of CNS neurons) and possibly facilitate their differentiation from neural stem cells.[7,25] Subcutaneous or intramuscular IFN-β products do not pass the BBB in significant amounts, even in people with MS,[3] thus the exploration of new routes of administration (such as nasal delivery), and reassessing the intrathecal administration that showed promising results in the '80 may uncover a yet unexploited therapeutic potential.[9]

Currently, there are four recombinant humanized IFN-β molecules approved for the treatment of relapsing MS (RRMS, SPMS): subcutaneous IFN-β-1b, subcutaneous IFN-β-1a, intramuscular IFN-β-1a and the more recently introduced subcutaneous PEGylated IFN-β-1a (PEG-IFN-β-1a). PEG-IFN-β-1a has a reduced renal clearance and a longer half-life compared with the classical IFN-β formulation, but similar bioavailability and pharmacokinetics[20,26] (see Table 1 for details on the commercially available pharmacological products). IFN-β-1a is also approved as a therapy for the first clinical events suggestive of MS, not yet fulfilling diagnostic criteria (clinically isolated syndrome).[9,20] No benefits were found in PPMS.[9,20] The pivotal and the subsequent clinical trials generally showed slightly better outcomes with PEG-IFN-β-1a (125 mcg q2wk) and also with the other subcutaneous formulations that have more frequent administration, namely IFN-β-1b (250 mcg every other day) and IFN-β-1a (44 mcg three times a week).[26–29] A comparative appraisal of these results is difficult (because of differences in study populations and methodologies) and the evidence from head to head trials is scarce, but typically all IFN-β-based drugs are considered to have similar overall efficacy, PEG-IFN-β-1a being the most cost-effective, even when compared with several higher efficacy DMT.[22,26–32] In some people with early

Table 1. Recombinant IFN-β drugs used in MS

Drug and recommended regimen	Trade/brand names and autoinjector devices	Pivotal trials	Approved indications	Side effects to monitor[10]
IFN-β-1b, 250 mcg/1 ml, (8 MIU of antiviral activity), subcutaneous, qad	Betaferon®/Betaseron® with/without Betaject® Comfort/Betacomfort® (mechanical autoinjector) or BETACONNECT™ (fully electronic autoinjector) and myBETAapp™; nb. Betaferon®/Betaseron® needs reconstitution (powder and solvent); generics are available: e.g. Extavia® with the Extavia® Auto-Injector II (mechanical)	The IMSG trial (phase III, multicenter, randomized, placebo-controlled, double-blinded; relapsing MS; 2-year follow-up)	Approved by FDA in 1993 for relapsing MS and by EMEA in 1995 for RRMS and subsequently for active SPMS	Common: • Dose-related flu-like syndrome, including fever, chills, fatigue, myalgia and headache (also exacerbation of primary headaches); these last up to 24 h after IFN-β administration and are mitigated by acetaminophen, non-steroidal anti-inflammatory drugs and appropriate IFN-β dose titration when starting the treatment • Injection site reactions ranging from mild (redness, pain) to severe (necrosis, ulcers, lipoatrophy); mild reactions occur in up to 90% with classical subcutaneous formulations and up to 50% for intramuscular and PEGylated IFN-β-1a; are mitigated by proper administration technique and local intervention Uncommon: • Liver toxicity (exceptional cases of fulminant liver failure and of exacerbation of autoimmune hepatitis are documented) • Autoimmune thyroiditis and other organ-specific autoimmune conditions • Depression/exacerbation of preexisting depression • Anemia, neutropenia, lymphopenia • Thrombotic microangiopathy and thrombocytopenic purpura with hemolytic uremic syndrome • Others: posterior reversible encephalopathy syndrome, infections
IFN-β-1a, 30 mcg/0.5 ml (6 MIU of antiviral activity), intramuscular, qwk	Avonex® prefilled syringe or Avonex PEN® (mechanical autoinjector, single dose/use, prefilled)	The MSCRG trial (phase III, multicenter, randomized, placebo-controlled, double-blinded; relapsing MS; 2-year follow-up)	Approved by FDA in 1996 and by EMEA in 1997 for relapsing MS; subsequently also approved for clinically isolated syndrome (first clinical event suggestive for RRMS but not yet fulfilling diagnostic criteria)	
IFN-β-1a (new formulation), 44 mcg/0.5 ml (12 MIU of antiviral activity), subcutaneous, tiw; 22 mcg/0.5 ml and 8.8 mcg/0.5 ml, subcutaneous, tiw (for titration)	Rebif® prefilled syringe with/without Rebject II® (mechanical autoinjector for prefilled syringes) or Rebif® Rebidose® (mechanical autoinjector, single dose/use, prefilled); an electronic autoinjector, RebiSmart® is also available	The PRISMS/PRISMS-2 trial (phase III, multicenter, randomized, placebo-controlled with two interventional arms; relapsing MS; 2-year follow-up); followed by a 2-year extension (PRISMS-4) and then by a phase IIIb trial (IMPROVE)	Approved by EMEA in 1998 and by FDA in 2002, initially for relapsing MS, subsequently also for clinically isolated syndrome; the new formulation was approved in 2007, with the same indications, and replaced the initial one (reduction in injection site reactions and lower immunogenicity/NAb)	
PEG-IFN-β-1a, 125 mcg/0.5 ml (12 MIU of antiviral activity), subcutaneous, q2wk; 94 mcg/0.5 ml and 63 mcg/0.5 ml (for titration)	Plegridy® prefilled syringe or Plegridy® Pen (mechanical autoinjector, single dose/use, prefilled, ready to use)	The ADVANCE trial (phase III, multicenter, randomized, placebo-controlled, double-blinded/delayed treatment; 2-year follow-up)	Approved in 2014 for	

IFN-β, beta interferons/interferon beta; MS, multiple sclerosis; RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis; MIU, million of International Units; IMSG, IFN-β multiple sclerosis study group; MSCRG, multiple sclerosis collaborative research group; EMEA, European medicines agency; FDA, food and drug administration; NAb, IFN-β neutralizing antibodies.

RRMS, besides decreasing the ARR, IFN-β also delays the time until sustained/confirmed disability accrual[26–32] and may provide benefits on long-term survival.[9,33,34] Other pharmacological products may have synergic or complementary effects with IFN-β, increasing their efficacy (and/or decreasing their side effects), but evidence is modest and combined therapy with IFN-β is not currently recommended.[7]

All IFN-β formulations have good long-term safety profiles. The side effects are similar among pharmacological products, the most common including injection site reactions and post-injection flu-like syndrome; potentially severe side effects that require biological and clinical monitoring (e.g. periodic complete blood count, liver enzymes and thyroid function tests, assessment for depression) are uncommon or very rare (Table 1). The good safety profile of IFN-β is shared across age groups and sexes, but efficacy may be lower in the geriatric populations and some ethnic groups.[9,20] Accumulating evidence shows that IFN-β do not impair conception and are generally safe for pregnant women and fetuses.[35]

As with other self-injectable drugs, long-term adherence and tolerability are related to the drug delivery burden (i.e. frequency of administration and administration-related side effects) and may have significant negative impact on the therapeutic efficacy and quality of life.[9] Mechanical and electronic autoinjector devices are more convenient to use, may mitigate injection site reactions and may increase adherence.[9,36] Concurrently, the electronic/smart devices allow for a more accurate adherence appraisal and are becoming increasingly available (see Table 1).[9,36]

According to the current European guidelines, all persons with active MS should be offered DMT, and people with MS with stable disease that have no safety or tolerability issues should be treated indefinitely.[20] Achieving prompt therapeutic control of the disease in the first years since clinical onset is associated with longer time until progressive disability accrual and slower rates of progression in relapsing MS,[37,38] and this suggests the existence of a window of opportunity for therapy. However, it is still unclear what treatment strategy is the most appropriate in MS: escalation (start with low potency drugs but with fewer adverse events, and incrementally move up to stronger DMT if disease activity) or induction (treat from the outset with high potency drugs, with the trade-off of more potential side effects).[9] It is becoming increasingly accepted that people with highly active MS at baseline, as well as those with breakthrough disease (relapses after apparent achieving therapeutic control), should be offered high efficacy DMT, increasing their chances of good long-term disability and quality of life outcomes.[19] However, current statements on DMT efficacy refer to statistical estimates for the whole populations from clinical trials and accurate methods for DMT personalization are currently lacking. Thus, the choice of the drug typically depends on the phenotype and the degree of activity of the disease, on the concurrent contraindications and safety concerns as well as the availability pharmacological products, local expertise and preference of the patient.[20]

Currently, there are no accurate tools for the early prediction of IFN-β treatment failure, however, some progress has been made with the development of the Rio criteria and the modified Rio criteria, which may be used after the first year of IFN-β therapy to predict the probability of suboptimal clinical outcomes over the next 2 years.[39] Multivariate targets that could be used to predict good long-term outcomes, such as the 'no evidence of disease activity' models are developed, but their utility outside clinical trials is not yet fully established.[40]

The existence of a small subgroup of people with MS with inborn or acquired impaired biological responses to exogenous IFN-β in the absence of IFN-β neutralizing antibodies (NAb), the so-called 'non-responders' is still debated.[6,41] Most people with MS have low baseline activity of IFN type I-dependant pathways.[5–9] The serum concentrations of IFN-α and IFN-β are also low, even below the level required for the immediate biological response (i.e. expression of the type I IFN regulated genes), which explains the reversible biological 'resistance' to exogenous IFN-β observed in *ex vivo* studies.[5,7,8] A minority of patients have 'normal' or increased baseline IFN-β levels and IFN type I activity, thus, pharmacological enhancement of type I IFN pathways may have no effect on an already saturated system or may even do harm. This should be interpreted cautiously, since endogenous IFN-β levels and pathways are subjected to significant fluctuations (e.g. increase in acute viral infections) and normal IFN-β levels do not prove integrity of the downstream processes.[6,42] Periodical assessment of the integrity of the biological response to IFN-β, e.g. by measuring the induction of MxA expression in PBMCs or by evaluating more complex functional IFN-β signatures or genetic markers, would help identify those people with MS that are unlikely to benefit from the initiation or continuation of IFN-β-based therapies, thus aiding DMT decision making.[18,41,42]

A cause of impaired biological response to pharmacological IFN-β is the presence of Nab, which may develop in up to a quarter of people with MS during the first years of IFN-β therapy.[42] A general consensus on NAb is not available, but pertinent strategies include testing at 12 and 24 months since the initiation of IFN-β, or if relapses occur.[29,42] NAb are specific to the pharmacological product but may cross-react, therefore if they are present in the context of breakthrough disease, switching to a non-IFN-β-based DMT is recommended.[9,20] Nab, as well as PEG antibodies, may also develop in people treated with PEG-IFN-β-1a, but to a lesser extent and seem to have no clinical relevance.[26]

IFN-*β* and COVID-19

COVID-19 is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), an emerging human virus that has rapidly spread since the end of 2019, resulting in a pandemic (still ongoing as of November 2020). The spectrum of clinical presentation ranges from asymptomatic to mild upper respiratory disease to severe pneumonia with acute respiratory distress syndrome, multiple organ failure and death. SARS-CoV2 induces type I IFN antiviral response *in vitro* and in animal models, but to a lesser extent than other viruses.[43] Studies suggest type I IFN response induced by SARS-CoV-2 is delayed and *in vitro* IFN-β administration successfully halts viral replication.[44] Impaired type I IFN response, resulting in diminished antiviral effects and increased expression of pro-inflammatory cytokines, was found in critically ill patients with COVID-19.[43–47] These are related to inborn deficiencies in type I IFN pathways (in at least 3% of patients with life-threatening COIVD-19)[45] and to direct effects of SARS-CoV-2, which, similar to other viruses, eludes the host's innate immunity by antagonizing type I IFN.[43,44,46,47] High serum levels of neutralizing immunoglobulin G autoantibodies against type I IFN, that blocks the endogenous anti-SARS-CoV2 response, are found in about 10% of the patients that develop life-threatening SARS-CoV2 pneumonia, prior to infection, and in none of those with asymptomatic or mild infection.[48] These autoantibodies are mainly against IFN-α and do not necessarily react with pharmacological

IFN formulations, but may have deleterious consequences if convalescent plasma from these patients is used as therapeutic resource in the treatment of others.[48] Their production is related to inborn errors of type I IFN immunity that were estimated to account for life-threatening SARS-CoV-2 pneumonia in at least 12.5% of males and 2.6% of females.[48] All of the above data provide a rationale for type I IFN-based therapies in selected patients with COVID-19. Preliminary results of randomized clinical trials support the effectiveness of some IFN formulations, especially IFN-β, alone or in combination with antiviral drugs.[49–52] A novel inhaled nebulized IFN-β-1a formulation has also been trialed and seems safe and possibly effective.[53]

The ongoing COVID-19 pandemic raises specific concerns for the MS population. Based on available data, and also supported by data from the previous outbreaks of novel coronaviruses (the acute respiratory syndrome coronavirus SARS-CoV in 2003; and the Middle East respiratory syndrome-related coronavirus in 2013), people with MS do not seem to be at increased risk of getting infected and only lymphocyte-depleting DMT seem to increase the risk of severe infectious disease outcomes.[54,55] Through their profile both as a drug for MS and in the context of COVID-19, IFN-β-based therapies are standing out through their safety profile, the speculative positive role in case of infection, and through their potential of non-interference with the efficacy of future SARS-CoV-2 vaccines.[55,56]

Conclusion

IFN-β are the first approved DMT for MS. Their overall risk-benefit profile and cost-effectiveness makes them still widely used, despite the availability of newer, more effective and/or non-injectable drugs. They have moderate efficacy in controlling disease activity and may improve long-term disability accrual in some people with early relapsing MS. The development of predictors of response or failure to IFN-β, prior to or early after treatment initiation, and identifying early responders to IFN-β in MS would allow for a more tailored treatment approach and maximize long-term outcomes. Last but not least, better understanding the potential therapeutic role of IFN-β in COVID-19 and other diseases caused by emerging viruses, would help build knowledge on the safety of different therapeutic options for people with MS in the context of future epidemics/pandemics.

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