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# Interferon beta-1a sc at 25 years: a mainstay in the treatment of multiple sclerosis over the period of one generation

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## ABSTRACT

**Introduction:** Interferon beta (IFN beta) preparations are an established group of drugs used for immunomodulation in patients with multiple sclerosis (MS). Subcutaneously (sc) applied interferon beta-1a (IFN beta-1a sc) has been in continuous clinical use for 25 years as a disease-modifying treatment.

**Areas covered:** Based on data published since 2018, we discuss recent insights from analyses of the pivotal trial PRISMS and its long-term extension as well as from newer randomized studies with IFN beta-1a sc as the reference treatment, the use of IFN beta-1a sc across the patient life span and as a bridging therapy, recent data regarding the mechanisms of action, and potential benefits of IFN beta-1a sc regarding vaccine responses.

**Expert opinion:** IFN beta-1a sc paved the way to effective immunomodulatory treatment of MS, enabled meaningful insights into the disease process, and remains a valid therapeutic option in selected vulnerable MS patient groups.

## ARTICLE HISTORY

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## KEYWORDS

Interferon beta-1a; multiple sclerosis; disease-modifying therapy; 25 years; generation; long-term efficacy; long-term safety; mechanisms of action

## 1. Introduction

Since our previous review of the knowledge base on interferon beta-1a for subcutaneous injection (IFN beta-1a sc) in multiple sclerosis (MS) 20 years after its regulatory approval in Europe [1], significant new data and evaluations have been published. The present article therefore provides a necessary update.

Interferons (IFNs) are signaling glycoproteins initially discovered as cytokines involved in antiviral defense mechanisms [2]. The advent of recombinant DNA technology enabled the development of IFN alpha-based medications as drugs primarily directed against viral diseases [3]. After the immunoregulatory potential of IFNs was recognized, IFN beta preparations followed as the first immunomodulatory treatment option for patients with MS [4].

IFN beta preparations are a group of disease-modifying therapies (DMTs) with one of the longest histories of use in people with MS. They were the first therapeutic agents that convincingly reduced the relapse rate and disability progression in patients with relapsing-remitting MS (RRMS), the first to show efficacy in secondary progressive MS (SPMS) with relapses, and the first to be used successfully and safely in pediatric patients with MS [5–7]. The therapeutic potential of IFN beta in this disease has been widely

attributed to the selective anti-inflammatory action via downregulation of the chronic overexpression of proinflammatory cytokines [8,9]. Recently, however, new evidence revived the previously prevailing hypothesis of an etiological role of herpesviridae, in particular Epstein-Barr virus (EBV), in the pathogenesis of MS [10–12] – refocusing the interest to the antiviral effects of IFN beta as mediators of its therapeutic potential in the disease [13].

IFN beta-1a sc has been in continuous clinical use for 25 years after its regulatory approval in Europe, i.e. for the full time span of one human generation. IFN beta-1a sc (Rebif®) received its marketing authorization on 4 May 1998 in Europe and on 8 March 2002 in the U.S.A.. The recommended dosage of IFN beta-1a is 44 µg three times weekly by subcutaneous injection. A reduced dose of 22 µg dose is recommended for patients who do not tolerate the higher standard dose [14]. The safety profile of IFN beta-1a sc is similar in children, adolescents, and adults [7], and the licensed indication covers a wide spectrum of patient ages. Since its introduction, the estimated cumulative exposure to subcutaneously injected glycosylated IFN beta-1a amounts to more than 1.9 million patient years [15].

While several drugs were licensed, introduced, and established in the meantime [16,17], IFN beta-1a sc remains a

### Article highlights

- Subcutaneously (sc) applied interferon beta-1a (IFN beta-1a sc) has been in continuous clinical use for 25 years as a disease-modifying treatment in patients with multiple sclerosis (MS).
- IFN beta-1a sc continues to provide benefit in a broad range of situations from the first symptoms of MS to secondary progressive MS and from young children to elderly adults with MS. It may be also used during pregnancy and the breastfeeding period if clinically required.
- Adherence to the prescribed regimen of IFN beta-1a sc is supported by the use of dedicated injection devices, which provide feedback to the patient based on the monitoring of actual drug applications.
- IFN beta primarily works by activating the Janus kinase/signal transducers and activators of transcription (JAK-STAT) signaling pathway, which modulates a wide range of biological activities, including antiviral defense and immune cell function.
- Recently, cross-sectional investigations on the intestinal microbiome in MS patients suggested that the therapeutic activity of IFN beta may involve changes in the composition and diversity of microbial communities inside the gut.
- Vaccination of MS patients being treated with IFN beta generally produces humoral and T-cell responses comparable to those observed in healthy individuals.
- Ongoing use of IFN beta is associated with a lower risk of severe COVID-19 than other disease-modifying treatments.

mainstay in the DMT of MS [18] based on extensive data from clinical studies and real-world use (Table 1, Figure 1). This is illustrated by the current prescription prevalence of IFN beta-1a preparations in Germany of 70.8 per 1000 MS patients (IFN beta-1b: 34.1) – in a range comparable to the oral DMTs teriflunomide (54.5) and fingolimod (63.8), while the overall DMT prescription prevalence in MS patients was 483 per 1000 in 2019 [41].

In our previous publication [1], we comprehensively reviewed the knowledge base on IFN beta-1a and IFN beta-1b in MS 20 years after their market introduction in Europe. Meanwhile, long-term experience with IFN beta-1a sc grew larger over a full generation as the early patients grew older. Moreover, significant progress was achieved regarding our understanding of the disease mechanisms of MS, and treatment approaches have been modified accordingly.

In the light of these developments, we provide a follow-up review covering data and insights on IFN beta-1a sc published since 2018 and after more than 25 years of extensive use in clinical practice. We discuss recent insights from the pivotal trial PRISMS and its long-term extension, data from randomized studies with IFN beta-1a sc as the reference, the use of IFN beta-1a sc across the patient life span, the support of adherence to the prescribed regimen, the use of IFN beta-1a sc as a bridging treatment, novel insights concerning the mechanisms of action, and potential benefits of IFN beta-1a sc regarding vaccination.

## 2. Insights from the pivotal trial PRISMS

The parameter NEDA (no evidence of disease activity) was introduced in 2012 to characterize the MS disease course. It has since been increasingly used as an efficacy endpoint in clinical trials on RRMS [42]. In a *post hoc* analysis of the pivotal study PRISMS

(Prevention of Relapses and Disability by Interferon beta-1a Subcutaneously in Multiple Sclerosis) initiated in the 1990s [24], efficacy was confirmed using different definitions of the endpoint NEDA [43]. The proportion of patients with status NEDA-3 (defined as the absence of relapses, 3-month confirmed disability progression, and active T2 lesions) in year 1 was 30.1% in the IFN beta-1a sc high dose (44 µg) group compared to 10.9% in the placebo group [43]. These low rates are consistent with characteristics of the PRISMS population that comprised patients with relatively high levels of disease activity (with an average of 3 relapses in the previous 2 years) as compared to more recent trials performed in RRMS patients (with, e.g. ~2 relapses on average in the ASCLEPIOS trials on ofatumumab published in 2022 [44]). In fact, over the last 25 years there has been a shift toward earlier use of IFN beta-1a preparations, i.e. in patients with less active MS, besides changes in the inclusion criteria of the clinical trials [45–48].

Of note, exploratory analyses of the original data from the first year of the PRISMS study revealed an early onset of therapeutic efficacy of IFN beta-1a sc: significant improvements of radiological and clinical endpoints were observed 2 and 3 months after treatment initiation, respectively [43]. These findings are in line with data from the placebo-controlled randomized IMPROVE study in 180 patients with active RRMS, showing that IFN beta-1a sc (44 µg three times weekly) has a beneficial impact on magnetic resonance imaging outcomes as early as 4 weeks after treatment initiation (reduction in the mean cumulative number of new gadolinium-enhancing lesions by 68%) [49]. A recent study showed that the treatment with sc IFN beta-1a reduces the number of new lesions evolving into black holes, while ventricular enlargement occurs in the first year of treatment, likely due to pseudo-atrophy [50].

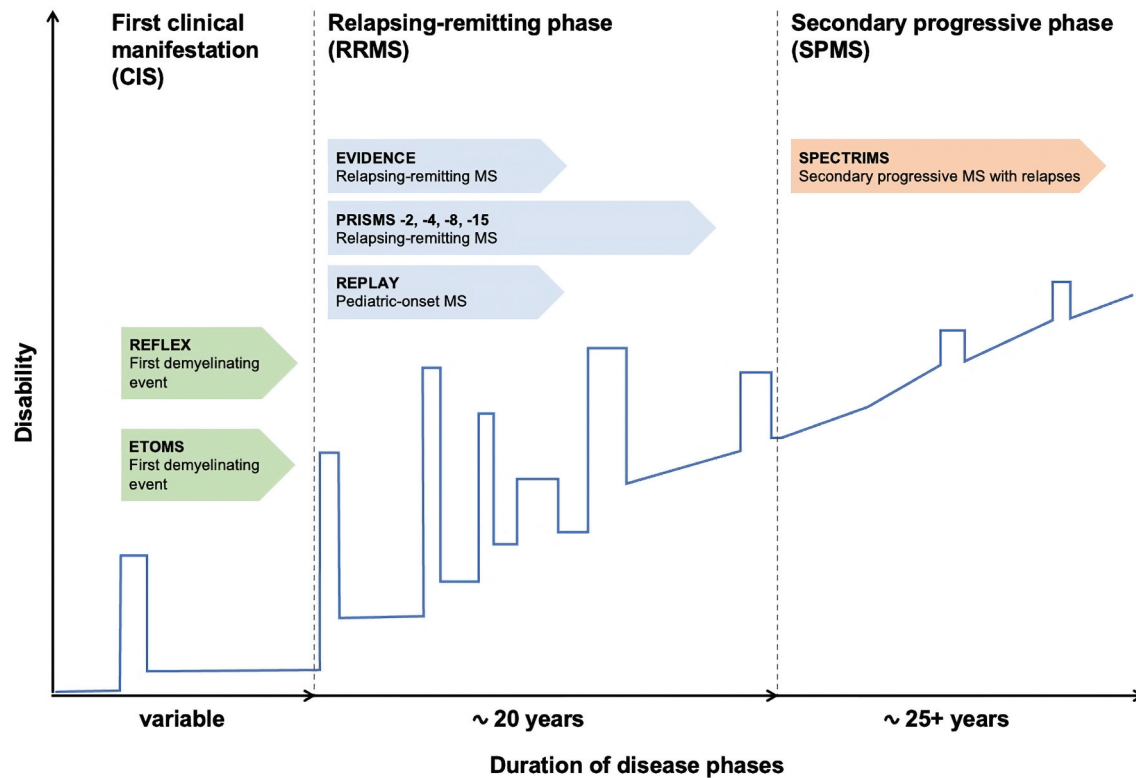
Using the criteria of the Magnetic Resonance Imaging in MS (MAGNIMS) network to categorize the disease course of RRMS patients in the PRISMS study population, Sormani et al. found a median time to clinical disease activity (CDA) of 2.6 years in patients with a MAGNIMS score of 0 after 1 year of therapy, while patients with higher scores experienced new disease activity earlier (median time to CDA 1.6 and 1.3 years with score 1 and 2, respectively) [51]. The median time to confirmed progression in the Expanded Disability Status Scale (EDSS) was 3.2 years in patients with a MAGNIMS score of 2 after 1 year of therapy, while the median was not reached during the 15–16 year observation period for the patient group with lower MAGNIMS scores of 0 or 1. The risk of progression was significantly lower in patients with a score of 1 versus 2 ( $p < 0.0001$ ), suggesting that the continuation of IFN beta-1a sc (44 µg) after 1 year of therapy is a valid treatment option for patients with a MAGNIMS score  $< 2$  at this point in time.

To achieve optimal efficacy, IFN beta appears to require an exposure beyond a certain threshold that may not be reached in all patients treated with the once weekly regimen licensed for intramuscular IFN beta-1a [52]. This notion is supported by a previous exploratory analysis of long-term data collected over 15 years in the PRISMS study (PRISMS-15) [25]: outcomes were compared in the lowest and highest quartile of the

Table 1. Therapeutic studies on IFN beta-1a sc in multiple sclerosis discussed in this review.

Name of Study (alphabetical order) [Reference]	Initial Number of Participants	Indication	Treatment(s)	IFN beta-1a sc Dosage	Primary Endpoint(s)	Major (primary) Results
COGIMUS [19]	331	RRMS	IFN beta-1a sc high dose and low dose	22 or 44 µg 3 × weekly	Cognitive impairment	Lower risk of cognitive impairment with higher dose Odds ratio .61
ETOMS [20]	308	CIS	IFN beta-1a sc low dose vs placebo	22 µg 1 × weekly*	Conversion to CDMS	
EVIDENCE [21]	677	RRMS	IFN beta-1a sc vs IFN beta-1a im	44 µg 3 × weekly	Proportion of relapse-free patients	IFN beta-1a sc superior to IFN beta-1a im
FUTURE [22]	50	Pediatric onset MS	IFN beta-1a sc via electronic injection device	22 µg 1 × weekly*	Self-reported quality of life (QoL)	Potential of improved psychosocial health and school functioning
IMPROVE [23]	180	RRMS	IFN beta-1a sc (new formulation) vs placebo	44 µg 3 × weekly	Number of active CNS lesions	Reduction by 69%
PRISMS, at 2, 4, 8 and 15 years of study [24–28]	560	RRMS	IFN beta-1a sc vs placebo	22 or 44 µg 3 × weekly	Relapse rate	Pivotal trial, supported early start of therapy and higher dosage
REBIFLECT [29]	731	RRMS	IFN beta-1a sc via electronic injection device	22 or 44 µg 3 × weekly	Adherence to prescribed regimen	97.9% quantitative adherence
REFLEX [30]	517	CIS	IFN beta-1a sc high vs low frequency vs placebo	44 µg 1 ×* vs 3 × weekly	Conversion to CDMS	Dose-dependent reduction vs placebo with both dosing regimens
REFLEXION [31]	402	CIS	IFN beta-1a sc early vs delayed	44 µg 1 ×* and 3 × weekly	Conversion to CDMS	Prolonged time to CDMS over 5 years
REGARD [32]	764	RRMS	IFN beta-1a sc vs glatiramer acetate	44 µg 3 × weekly	Relapse rate, number of active CNS lesions number of active CNS lesions	Fewer Gd-enhancing lesions on IFN beta-1a sc vs glatiramer acetate
REPLAY [33]	307	Pediatric onset MS	IFN beta-1a sc	22 or 44 µg 3 × weekly	Safety and tolerability in pediatric patients	Reduction of relapse rate by 74%
SMART [34]	912	RRMS	IFN beta-1a sc using an electronic injection device	22 or 44 µg 3 × weekly	Adherence to prescribed regimen	97% cumulative adherence
SPECTRIMS [35]	618	SPMS with relapses	IFN beta-1a sc high dose vs low dose	22 or 44 µg 3 × weekly	Confirmed disability progression	Pivotal trial, resulted in licensing for SPMS with relapses
<b>Clinical studies of interest with IFN beta-1a sc as the reference treatment</b>						
CAMMS223 [36]	334	RRMS	Alemtuzumab vs IFN beta-1a sc	44 µg 3 × weekly	Sustained accumulation of disability, relapse rate	Hazard ratio .29 and .26, respectively
CARE-MS I and II [37,38]	1248	RRMS	Alemtuzumab vs IFN beta-1a sc	44 µg 3 × weekly	Relapse rate	Lower relapse rate with alemtuzumab
OPERA I and II [39]	1656	RRMS	Ocrelizumab vs IFN beta-1a sc	44 µg 3 × weekly	Relapse rate	Lower relapse rate with ocrelizumab
TENERE [40]	324	RMS	Teriflunomide vs IFN beta-1a sc	44 µg 3 × weekly	Time to confirmed failure (relapse or permanent discontinuation)	Comparable time to failure

\* This dosage is not licensed for clinical use.  
 CDMS = clinically definitive multiple sclerosis; CIS = clinically isolated syndrome; CNS = central nervous system; Gd = gadolinium; IFN = interferon; im = intramuscular; MS = multiple sclerosis; RRMS = relapsing-remitting multiple sclerosis; sc = subcutaneous; SPMS = secondary progressive multiple sclerosis; RMS = relapsing forms of multiple sclerosis.



**Figure 1.** Key clinical studies with IFN beta-1a sc covering the full spectrum of relapsing MS course types and disease durations [20,21,24–26,28,30,33,35]. CIS = clinically isolated syndrome.

cumulative sc IFN beta-1a dose groups. Higher cumulative dose, longer time on treatment, and higher treatment adherence appeared to be associated with better outcomes in patients with RRMS. Among the patients with longer mean time on IFN beta-1a sc therapy (14.7 years, highest quartile), 86% did not reach an EDSS score of 6.0 or higher compared to 48% of the patients with shorter mean time on IFN beta-1a sc treatment (2.9 years, lowest quartile) [25]. Similarly, exposure to higher cumulative doses of IFN beta-1a sc was associated with lower proportions of patients experiencing 3-month confirmed progression in the EDSS (52.8% versus 68.5%) and/or conversion to SPMS (20.8% versus 52.1%), while each additional 5 years on treatment were correlated to a 13% lower risk of relapse (hazard ratio 0.87) [25]. Moreover, patients with worse outcomes may have been more likely to discontinue or switch the treatment. These findings suggest that in patients with active MS, IFN beta-1a sc is capable of reducing the risk of disease progression over prolonged periods of time. We elaborate on the underlying mechanisms of action in section 5.2 of this review.

### 3. Data from recent clinical studies with interferon beta-1a sc as a comparator

Besides 25 major clinical studies, including seven phase III trials and comprising a total of > 6500 patients [15], IFN beta-1a sc has been widely used as a reference in randomized clinical trials that investigated drug candidates which are today considered highly effective. Beyond pivotal data on

the novel treatment options, these studies provided valuable information on IFN beta-1a sc.

In a *post hoc* analysis of the pivotal studies OPERA I and II [39] of ocrelizumab in RRMS, the proportion of patients with 24-week composite confirmed disability accumulation (CDA) due to progression independent of relapse activity (PIRA) was 80.6% in the IFN beta-1a sc group (137 of 170 events) compared to 89.1% in the ocrelizumab group (115 of 129 events) [53]. In the IFN beta arm, CDA was more often due to relapse-associated worsening. The overall event rates were lower in the ocrelizumab group versus the IFN beta-1a sc (44 µg) group, primarily driven by the pronounced effect of ocrelizumab on acute inflammatory events. Accordingly, the percentage of patients with NEDA after the 96-week treatment period was 47.7% in the ocrelizumab group and 27.1% in the IFN beta-1a sc group [54]. Subgroup analyses, however, showed an increased probability of the status NEDA with age: Among those patients who were randomized to IFN beta-1a sc, the proportion with NEDA was higher in the subgroup aged 40 years or older versus younger patients (33.7% vs. 22.6%) [54].

Similar to these results, 89% of patients treated with IFN beta-1a sc remained free of 6-month confirmed disability progression during the two-year observation period in the CARE-MS I trial on alemtuzumab [37]. This percentage was comparable to the percentage of 92% reported for the group that received the antibody therapy. The mean EDSS score improved from baseline by 0.14 points in both groups [37].

A recent Bayesian network meta-analysis revealed a rate ratio of annualized relapse rate and hazard ratios of time to 3-month and 6-month confirmed disability progression for the treatment with IFN beta-1a sc (44 µg) versus placebo of 0.64, 0.66 and 0.78, respectively [55]. Orally applied DMTs tended toward lower relapse rate ratios and similar progression hazard ratios compared to IFN beta-1a sc (44 µg) [55]. However, these results should be interpreted with caution due to differences in the populations included in these trials that were performed in a total time span of more than three decades. In a direct comparison of IFN beta-1a sc with an oral DMT, the phase 3 TENERE trial found a similar adjusted annual relapse rate in the study group treated with the higher dosage of teriflunomide (14 mg) versus IFN beta-1a sc in relapsing MS (0.26 vs. 0.22) [40].

While two prospective randomized trials (SENTINEL [56] and ONWARD [57]) investigated combinations of IFN beta-1a with natalizumab and cladribine, respectively, this path of development has not been followed any further predominantly due to safety concerns and limited magnitude of the expected effects versus monotherapy.

## 4. Interferon beta-1a sc across the patient life span

### 4.1. Treatment of pediatric/juvenile MS patients

Few disease-modifying medications have been licensed for the treatment of MS in pediatric patients. In Germany, IFN beta-1a remains the most frequently used DMT in children and adolescents with MS [58]. In the U.S.A., pediatric patients were more likely to receive other DMTs prior to starting IFN beta-1a sc, and they stayed on treatment with IFN beta-1a sc for a shorter time compared to other regions of the world [59]. In 2016–2017, 48% of those aged >12 years and 70% of those <12 years started an injectable first-line therapy with either glatiramer acetate or IFN beta. Commonly used oral or intravenous therapies initially prescribed for pediatric MS in the US include dimethyl fumarate, natalizumab, rituximab, fingolimod, and teriflunomide [60].

The drug was prospectively investigated in juvenile MS patients and has a similar safety profile in adult and pediatric populations [61]. However, the safety and efficacy of IFN beta-1a sc in children below 2 years of age have not yet been established, and it should not be used in this age group [62].

A retrospective study published in 2013 reported on clinically useful efficacy of IFN beta-1a sc in juvenile RRMS patients in terms of a substantial reduction of the annualized relapse rate from 1.79 before to 0.47 on treatment [33]. The FUTURE study [22] revealed quality of life improvements in adolescent RRMS patients ( $n=50$ ) who received treatment with IFN beta-1a sc (22 µg) using the RebiSmart™ electronic autoinjection device. The parent-reported and the adolescent self-reported PedsQL4.0 scores (with the exception of emotional functioning), the psychosocial health summary score, and school functioning measures increased significantly over a 52-week period [22].

### 4.2. IFN beta-1a sc and reproductive health

No effects of IFN beta-1a sc on male fertility, sexual potency, or libido are known from human and animal studies. Given a 3 : 1 (female/male) sex ratio of MS patients [63,64] and a median age at disease onset of approximately 33 years [65], the therapeutic management during pregnancy and the breastfeeding period is a common issue [66,67]. The EU label of IFN beta-1a sc includes the explicit statement that it can be considered during pregnancy [62,68], and the US label includes data that help healthcare providers weigh treatment risks. Extensive experience from registries and post-marketing cohort studies support this notion: there is no evidence for an increased risk of severe congenital abnormalities or spontaneous abortions after exposure to IFN beta during the 6 months before conception or during pregnancy [69–72]. If clinically required, IFN beta-1a sc may be considered during pregnancy [73], e.g. in patients at risk of a rebound of disease activity after discontinuation of fingolimod [74].

According to an evaluation of data from the German Multiple Sclerosis and Pregnancy Registry, exposure to IFN beta via breast milk does not increase the risk of common adverse outcomes in the first year of life. The authors concluded that IFN beta preparations can be used during the breastfeeding period [75], a notion that is reflected in the current label [62].

### 4.3. Use of IFN beta-1a sc after a first demyelinating event

In a *post hoc* evaluation of data from the REFLEX trial in patients with a first demyelinating event (i.e. a clinically isolated syndrome, CIS) [30], early initiation of treatment with IFN beta-1a sc 44 µg three times weekly was associated with a higher likelihood of achieving the status NEDA-3 at 2, 3, and 5 years of therapy [76]. The odds of NEDA-3 were higher with IFN beta-1a sc 44 µg injected three times weekly versus once weekly at year 3 (odds ratio [OR] 2.26;  $p=0.024$ ) and year 5 (OR 3.22;  $p=0.048$ ) – consistent with the studies EVIDENCE [21] and PRISMS [24].

Battaglini et al. used subtraction imaging analysis to evaluate the spatial distribution of inflammatory activity in the brain over two years after CIS [77]. Treatment with IFN beta-1a sc reduced the development of new/enlarging lesions compared with placebo (mean number: 6.9 vs 10.9;  $p<0.01$ ), and this effect was primarily observed in brain regions with presence of high inflammatory activity, which included the anterior thalamic radiation.

### 4.4. Efficacy in transition from RRMS to SPMS

Regardless of the phenotypic categorization of the individual disease courses, diffuse neuroinflammation and neurodegeneration appear to be involved in the pathological mechanisms of any type of MS, while degenerative processes gain increased relevance once the disease has entered the progressive phase [78–80]. In a *post hoc* analysis of data from the PRISMS and SPECTRIMS studies, treatment with IFN beta-1a sc delayed disability progression in a subgroup of MS patients

who were in apparent transition from RRMS to SPMS [81]. Therefore, patients with active disease and/or progressive worsening of disability may benefit from continued therapy with IFN beta-1a sc. Data from SPECTRIMS had also suggested a potential sex effect with a significant delay of confirmed disability progression in female but not male patients [35], potentially due to hormonal factors [82].

In Europe, IFN beta-1a sc is licensed for use in patients with relapsing MS, which subsumes RRMS and SPMS with relapses [6,14]. Similarly, according to the US Food and Drug Administration label, IFN beta-1a sc is indicated for the treatment of patients with relapsing forms of MS to decrease the frequency of clinical exacerbations and delay the accumulation of physical disability, whereas efficacy of IFN beta-1a sc in chronic progressive MS has not been established [83].

#### 4.5. Treatment of MS patients at higher age

Treatment with IFN beta preparations is comparatively common in older MS patients. In a recent analysis of data from 10 treatment centers participating in the MS-PATHS alliance, these drugs were the most commonly used DMTs in RRMS patients at  $\geq 60$  years of age (17.6%) [84], an age group that is usually not represented in clinical studies [48]. Based on data from a large patient cohort ( $n = 5340$ ) treated with IFN beta-1a sc, Allignol et al. reported similarly high rates of relapse-free patients at 1 year after treatment initiation (94.1–95.4%) in patients of all age groups [85]. While this result may be biased by the age-related decrease of inflammatory disease activity and the increasing risk of conversion to SPMS in older patients, it suggests that the effectiveness of IFN beta-1a sc on inflammatory disease activity is preserved with increasing age and also among higher-age groups in the real-world setting, while disability progression was not addressed in this study.

An analysis of the long-term effectiveness of IFN beta and glatiramer acetate demonstrated that the benefits seen in the short-term are maintained over a 10-year period [86]. However, the treatment effect appeared to decrease over time, which is consistent with a meta-analysis showing that efficacies of immunomodulatory DMTs on disability progression are generally higher in younger patients than in older patients [87]. The driving factor remains unclear, but subgroup analyses suggested better treatment effects in those patients treated earlier and at lower EDSS scores [86].

Recently, treatment with IFN beta for  $>3$  years has been shown to be associated with significantly reduced all-cause mortality by 56% in a large sample of patients over 10 years of follow-up as compared to no or minimal exposure to IFN beta ( $<6$  months) [88].

#### 4.6. Neuropsychological aspects of MS

It is long-established that fatigue, cognition, and quality of life may be affected by the MS itself and the disease-modifying medication [89,90]. The CONFIDENCE study performed in 165 RRMS patients treated with IFN beta-1a in routine clinical practice provided evidence for a longitudinal association between depression and low cognitive status [91]. A meta-

analysis including 41 studies could not find any DMT that improved cognitive test performance more effectively than IFN beta [92]. Cognitive game training was shown to have a beneficial effect on cognitive performance in IFN beta-treated MS patients suffering from mild cognitive impairment [93]. Moreover, significantly better quality of life scores were reported for patients using IFN beta as compared to those taking teriflunomide with regard to the Mental Composite Score (MCS), the Patient-Reported Indices in MS (PRIMUS) assessment, and the Fatigue Severity Scale (FSS) [94]. However, to our knowledge, no further evidence from controlled randomized studies regarding the effects of IFN beta-1a sc on neuropsychological parameters has been published since our first review on IFN beta-1a sc from 2018 [1].

### 5. Recent information to be considered in the counseling of MS patients

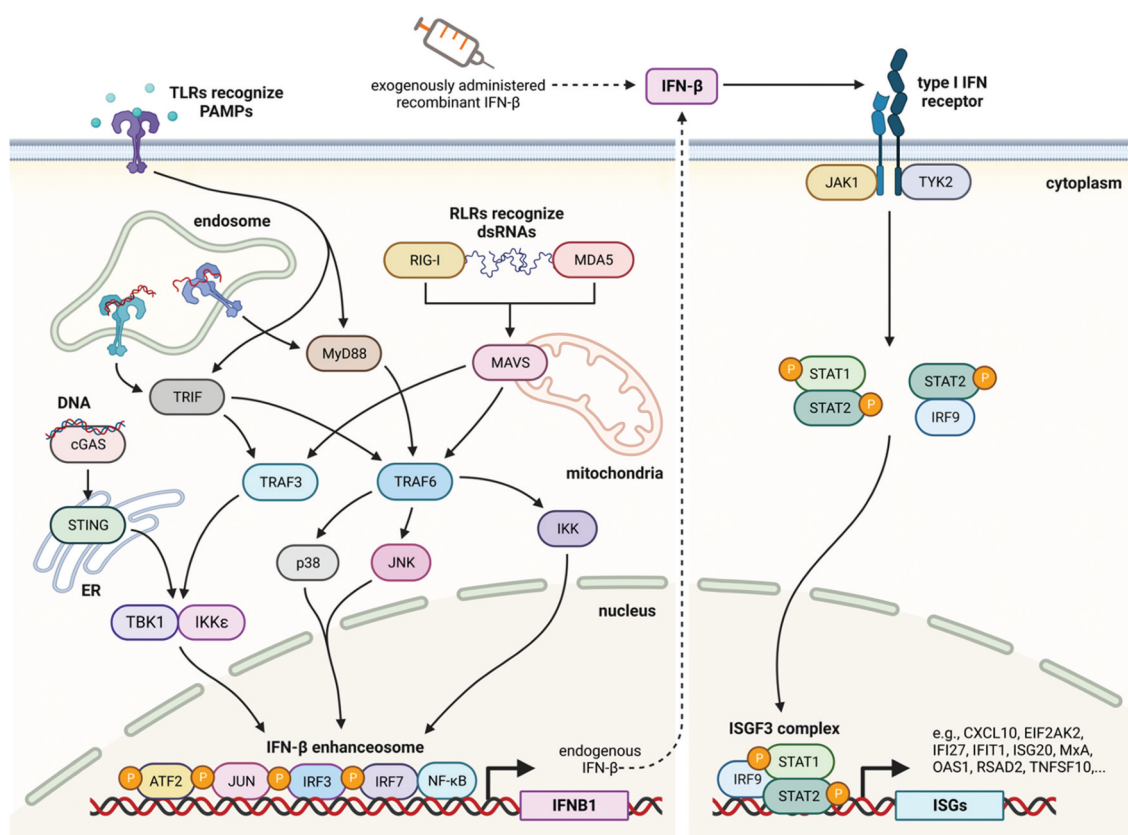
#### 5.1. Intracellular mechanisms of IFN beta signaling

The pathophysiology of RRMS is associated with an aberrant type I IFN response [95], which is thought to be at least partly mediated by the downregulation of the stimulator of interferon genes (STING)/IFN beta-axis. IFN beta primarily works by activating the Janus kinase/signal transducers and activators of transcription (JAK-STAT) signaling pathway: binding of IFN beta to the type I IFN receptor causes the phosphorylation of STAT1 and STAT2 followed by the formation of STAT1-STAT2 heterodimers. These dimers translocate to the cell nucleus, bind to the IFN-stimulated response element (ISRE), and modulate the expression of ISRE-regulated genes [8,96]. The cellular response to IFN-mediated signals is highly complex and encompasses changes in the expression of more than 500 genes and microRNAs [97–100] (Figure 2).

Recent evidence indicates that the type I IFN signaling can also be regulated by members of the Nod-like receptor (NLR) family [104] and that the cross-talk between components of the JAK-STAT pathway and those of other pathways is complex [105]. Hubel and coworkers used mass spectrometry to comprehensively explore the organization of the protein-interaction network between IFN-stimulated genes and other cellular proteins, thereby illuminating a wide range of biological activities [106].

#### 5.2. Insights regarding the mechanisms of action of interferon beta

The type I IFN signaling system has a major role in homeostasis and function of the immune system. The early interest in IFNs as a therapeutic option in MS was primarily motivated by their antiviral activities. Subsequently, as the immunomodulatory and antiproliferative properties of IFNs were discovered, the focus shifted to these regulatory features. Treatment with IFN beta thus rebalances the immune system in MS patients via highly pleiotropic effects, acting on various immune cells and molecular mediators, as previously described elsewhere [107–112]. IFN beta modulates the levels of matrix metalloproteinases, adhesion molecules, and integrins, thus preventing T cell/endothelial cell adhesion and the



**Figure 2.** Induction of type I interferon (IFN) responses and the JAK-STAT signaling pathway.

IFN beta is a naturally occurring cytokine produced by various cell types upon recognition of pathogen-associated molecular patterns (PAMPs) such as viral double-stranded (ds) RNAs by membrane-bound Toll-like receptors (TLRs), cytoplasmic RIG-I-like receptors (RLRs) or cyclic GMP-AMP synthase (cGAS) [8,101]. The TLRs signal via TRIF-dependent and MyD88-dependent pathways through TRAF3 and TRAF6. This leads to the activation of IFN regulatory factors (IRFs), nuclear factor- $\kappa$ B (NF- $\kappa$ B), JUN and activating transcription factor 2 (ATF2) [102]. The RNA helicases RIG-I and MDA5 use MAVS as mitochondrial adaptor protein, which functions like TRIF and activates the same transcription factors [101]. Moreover, cytosolic DNA derived from self and foreign sources causes activation of IRF3 via cGAS and the ER-anchored adaptor protein STING [95,103]. The activated transcription factors translocate from the cytoplasm to the nucleus and induce the transcription of IFN beta (shown on the left). Released IFN beta proteins as well as therapeutic IFN beta specifically bind the heterodimeric type I IFN receptor that is associated with two tyrosine kinases, TYK2 and JAK1 (shown on the right). Further requirements of a type I IFN response in target cells are STAT1 and STAT2, which are phosphorylated in response to signaling, and IRF9 [96]. The assembled transcription factor complex is bound to specific promoter elements and thereby induces the expression of hundreds of IFN-stimulated genes (ISGs) that confer the effects shown in Figure 3.

AP-1 = activator protein-1; ER = endoplasmic reticulum; GMP-AMP = guanosine monophosphate-adenosine monophosphate; IKK = inhibitor of NF- $\kappa$ B kinase; ISGF3 = IFN-stimulated gene factor 3; JAK = Janus kinase 1; JNK = Jun N-terminal kinase; JUN = transcription factor AP-1 subunit Jun; MAVS = mitochondrial antiviral signaling protein; MDA5 = melanoma differentiation-associated 5; MyD88 = myeloid differentiation primary response gene 88; p38 = p38 mitogen-activated protein kinases; RIG-I = retinoic acid-inducible gene I; STAT1 = signal transducer and activator of transcription 1; STAT2 = signal transducer and activator of transcription 2; STING = stimulator of interferon genes; TANK = TRAF family member-associated NF- $\kappa$ B activator; TBK1 = TANK-binding kinase 1; TRAF3/6 = tumor necrosis factor receptor-associated factor 3/6; TRIF = TLR adaptor molecule 1.

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migration of leukocytes across the blood-brain barrier [111]. These mechanisms are thought to reduce inflammation and further damage to the central nervous system, even though various effects remain to be fully elucidated.

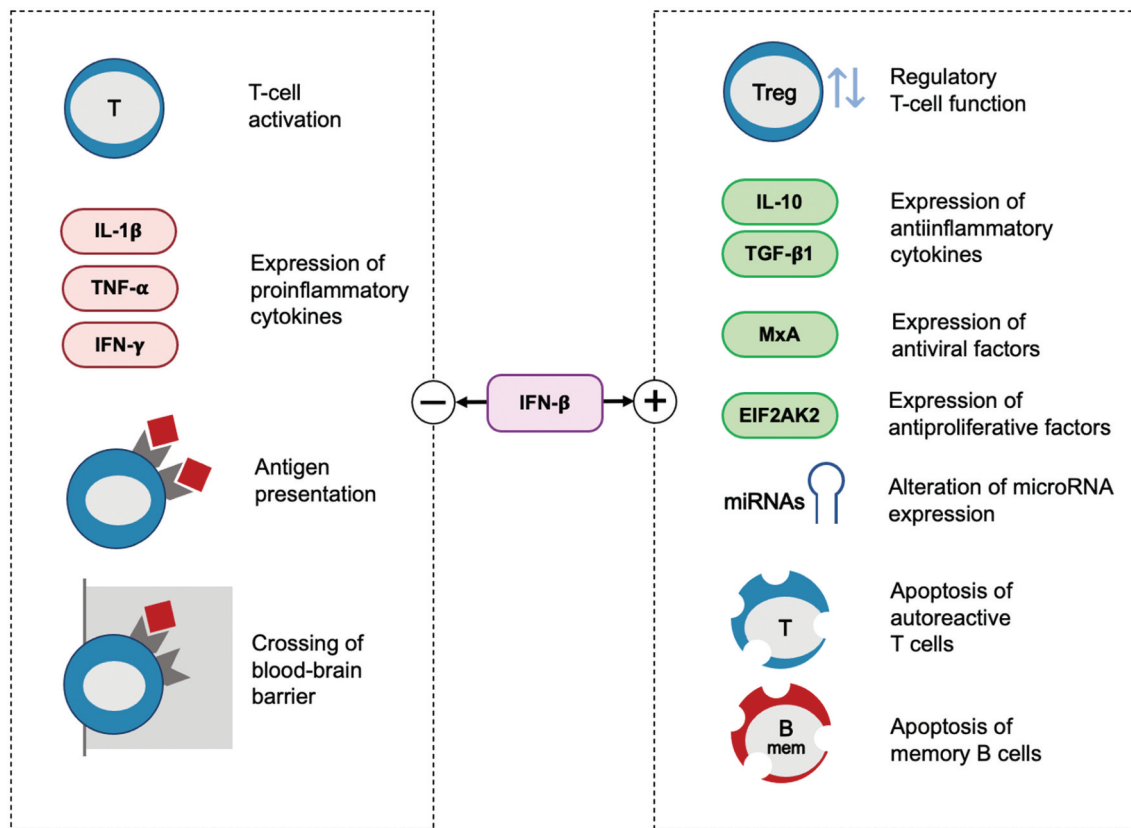
IFN beta is known to reduce the number of activated T cells. It promotes the expansion of regulatory T cells and supports their ability to suppress immune responses. Moreover, it increases the production of anti-inflammatory cytokines and decreases the production of pro-inflammatory cytokines. It also affects antigen presentation to T cells and promotes apoptosis of memory B cells (Figure 3). The latter was shown to be induced in response to IFN beta therapy via a mechanism requiring Fas (FS-7-associated surface antigen/CD95)-receptor/TACI (transmembrane activator and calcium-modulator and cyclophilin ligand interactor) signaling and enhanced production of apoptosis markers (such as annexin-V and caspase-3) [112]. Given the mounting evidence of a pivotal role of B cells in

the immunopathology of MS, targeting these cells is increasingly perceived as a key feature of DMTs [113].

Recently published research illustrated specific previously unrecognized effects of IFN beta that may be implicated in its therapeutic potential as well (Table 2). In a transcriptome profiling study performed in blood cells, long-term treatment with IFN beta was – among a multitude of other effects – associated with enhanced expression of genes involved in the oligodendroglia-protective integrated stress response and neuroprotection [114]. The functional viability of oligodendroglia is vital for myelin integrity, and remyelination is explored as an approach to restore or preserve neurological functions in MS [120].

Effects on microglial and dendritic cell functions were discussed as further potential modes of action [115,116], consistent with the observation of anti-inflammatory and positive cognitive effects of IFN beta-1a in a rat model of Alzheimer's disease and in a human pilot study [121,122].





**Figure 3.** Mechanisms of action of IFN beta.

In section 5.2 of the main text, we focused on new insights, as more detailed information on the principal mechanisms of actions illustrated here has already been covered in previous articles [107–112].

EIF2AK2 = eukaryotic translation initiation factor 2 alpha kinase 2; IFN = interferon; IL = interleukin; mem = memory; miRNA = microRNA; MxA = myxovirus resistance protein; RNA = ribonucleic acid; TGF = transforming growth factor; TNF = tumor necrosis factor; Treg = regulatory T cell.

**Table 2.** Effects of IFN beta with recently described potential therapeutic relevance in multiple sclerosis.

- Enhanced expression of genes involved in the oligodendroglia-protective integrated stress response and neuroprotection [114]
- Effects on microglial and dendritic cell functions [115,116]
- Antiviral activity, e.g. toward human herpes viruses such as Epstein-Barr virus [13]
- Modulation of microbiome composition [117]
- Support of survival and immunomodulatory functions of induced regulatory T cells [118]
- Improvements in the vascular reactivity of brain blood vessels [119]

The well-established antiviral effects of IFN beta are increasingly discussed as adjunct therapeutic mechanisms of action [13]. Recent research appears to support the long-suspected role of EBV in the pathogenesis of MS, increasingly pointing to late infection with EBV – at an age of 10 years or later – as a crucial trigger and driver of the development of MS [11,123–125]. EBV increases the survival of memory B cells [126,127] and causes long-lasting changes in host cytokine responses [124]. While the precise mechanisms of the involvement of EBV – and potentially other herpes viruses – in MS pathology remain to be fully elucidated, it may involve cross-reactions of immune responses against the viral antigen EBNA1 with auto-antigens in the CNS [128–130].

Disparate compositions of the intestinal microbiome have also been observed in untreated MS patients versus healthy controls [131] and in patients with PPMS versus patients with RRMS [132]. The involvement of the gut-microbiota-brain axis and alterations of the microbiome are increasingly discussed in the context of the pathogenesis of MS [133]. Recently, cross-sectional investigations on the intestinal microbiome in MS patients suggested that the therapeutic activity of IFN beta may involve changes in the composition and diversity of microbial communities inside the gut [117]. These changes may at least partially be mediated via the IFN beta-induced upregulation of short-chain fatty acid transporters located in the intestinal mucosa [131,134].

*In vitro* data further suggest that IFN beta supports the survival and immunomodulatory functions of induced regulatory T cells that stem from naïve CD4<sup>+</sup> cells [118]. According to another recent investigation, IFN beta treatment is associated with the expansion of regulatory T-cell subsets with high suppressive activity [135]. As this effect was found to be most pronounced in clinically stable patients, it may constitute a therapeutic mechanism of action.

One study suggests that the initiation of treatment with IFN beta-1a sc is associated with improvements in the vascular reactivity of brain blood vessels – a critical factor for neuronal

integrity [119]. This effect may be mediated by reduced inflammation and modulation of vasodilatory mediators. In this way, IFN beta may help mitigate neurodegenerative processes.

### 5.3. Predictive identification of treatment responders

Myxovirus resistance protein A (MxA) expression in blood is a marker of IFN beta bioactivity. In a cohort of 116 patients with early RRMS, low baseline MxA mRNA levels were strongly associated with the occurrence of  $\geq 9$  T2 lesions ( $p=0.012$ ) and a higher number of relapses ( $p=0.029$ ) during long-term follow-up (median: 11 years) [136]. Although a previous study could only show an association between low MxA mRNA levels and the relapse rate (follow-up: 5 years) in patients treated with intramuscular IFN beta-1a [137], these data may support the involvement of low levels of endogenous IFN beta in the occurrence of MS disease activity. This notion is in keeping with the previous observation that patients with a higher capacity for MxA induction at 3 months of therapy with IFN beta are more likely to respond to this treatment option [138].

In an analysis of data generated during the REFLEX and REFLEXION trials on IFN beta-1a sc in patients with a first demyelinating event, neopterin, soluble TRAIL (tumor necrosis factor-related apoptosis-inducing ligand), and IP-10 (interferon gamma inducible protein-10) measured in blood were confirmed as pharmacodynamic biomarkers associated with the effect of long-term treatment over 5 years [139]. Similarly, in patients with SPMS, treatment response (i.e. stabilization of the EDSS score for at least 2 years) was shown to correlate with the expression levels of a set of IFN-inducible genes [140]. It was also shown that IFN beta administration induces the production of the soluble IFN beta receptor isoform (sIFNAR2) in RRMS and that higher levels of sIFNAR2 might be associated with a reduced therapeutic response [141]. Thus, levels of sIFNAR2 could be measured to monitor an effective response to IFN beta therapy.

Neutralizing antibodies (NAbs) directed against the therapeutic agent may appear in a subset of treated patients with any protein-based drugs, including recombinant IFN beta. NAbs directed against IFN beta may first appear as late as 2 years after treatment initiation, and they may disappear over time if NAb titers remain low [142]. Pivotal studies of IFN beta preparations in MS reported negative effects of NAbs in patients with longer treatment duration [143], and there is consensus that high persistent titers of NAbs indicate the loss of biological effectiveness and an absence of therapeutic efficacy, suggesting a change of treatment [143,144]. However, the biological factors predisposing an individual to develop NAbs remain to be further elucidated [145,146].

Several pharmacogenetic studies have been performed to identify single-nucleotide polymorphisms with potential influence on the individual response to IFN beta therapy [147–150]. In a systematic review by Hocevar et al., 40 studies were identified that investigated the association between genetic variation and treatment response to IFN beta (5 genome-wide association studies and 35 candidate gene studies) [151]. Although the studies often lack consistency – due to various study designs, differences in definitions of responders and non-responders,

insufficient sample sizes and small effect sizes – there is evidence of a polygenic nature of IFN beta treatment response.

### 5.4. Injection devices and the adherence to the prescribed regimen

For the DMT of chronic diseases including MS, adherence to the prescribed regimen is a critical success factor regarding long-term disease outcomes [152], including durable treatment response and resource utilization [153–156]. In patients on treatment with frequently injected drugs, adherence is supported by the use of dedicated injection devices, which provide feedback based on the monitoring of actual drug applications [34]. For IFN beta-1a sc, several injection devices have been developed and introduced since its market introduction.

In the prospective observational study REBIFLECT [29], quantitative adherence to the prescribed regimen of three injections per week (using the RebiSmart® 2.0 device) was high and stable over time: a mean 97.9% of prescribed doses was injected over 2 years. Using the identical definition and the same device, the CONFIDENCE study group reported ~99% adherence among the patients who remained in the study (56 out of 165 patients after 36 months) [91]. Further data from recent prospective observational studies (READOUTsmart [157], GEPAT-SMART [158], DORADA [159] and others [160–162]) also suggest favorable patient experiences with the dedicated injection devices (RebiSmart® and RebiSmart® 2.0) that provide an electronic documentation of injections. However, the data from these observational studies should be interpreted with caution due to substantial patient attrition rates over time, which also varied across the studies.

A recently introduced third-generation injection device (RebiSmart® 3.0) enables the wireless transfer of injection data to mobile electronic devices, thus providing seamless real-time integration of injection data into comprehensive eHealth systems [163]. Overall, this approach may translate into optimized efficacy and enable longer periods of disease stability before a therapeutic escalation is required.

### 5.5. Use of IFN beta-1a sc as a bridging treatment

The long-term use of highly effective MS therapies may be limited by undesired effects on immunocompetence, e.g. reduced immunoglobulin levels on treatment with drugs directed against the CD20 lymphocyte surface antigen [164] or the time-dependent increase of the risk of progressive multifocal leukoencephalopathy in patients treated with natalizumab [165]. Concerns about drug exposure during pregnancy still prevail for some DMTs [166] (see section 4.2). Therefore, temporary or definitive de-escalation approaches using drugs with less sweeping effects, including IFN beta-1a sc, have been repeatedly considered and tested [167,169,170]. In patients who stop high-efficacy therapies associated with rebound activity after discontinuation [74], bridging with injectable immunomodulatory drugs (IFN beta or glatiramer acetate) may be considered as an option [171].

### 5.6. Potential benefits of IFN beta-1a regarding vaccine responses

While no associations between clinically overt infections and the risk of an MS relapse were observed in a recent prospective study [172], protecting MS patients from infections is still important to prevent potentially serious and prolonged sequelae [168]. Overall, IFN beta-1a sc is among the DMTs with the least detrimental effects on vaccine efficacy, as immunization with inactivated vaccines generally produces robust immune responses in IFN beta-treated patients [173]. Interferon beta preparations therefore are considered the *de facto* reference standard for studies on vaccine responses in MS patients on treatment with immunomodulatory drugs. In contrast, antibody production could be impaired in MS patients treated with disease-modifying drugs that affect the numbers and/or functions of B cells, including anti-CD20 antibodies [174].

In a prospective study on the vaccination against influenza virus in MS patients, no significant differences in the rates of protection against the H1N1 subtype were observed in participants treated with IFN beta-1a as compared with control subjects at 3, 6, and 12 months [175]. This result is consistent with findings from other studies on the efficacy of influenza vaccines, indicating that treatment with IFN beta-1a sc does not attenuate humoral or cellular responses [176–178].

The coronavirus disease-2019 (COVID-19) pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) prompted an unprecedented acceleration in the development and worldwide use of novel vaccines [179,180]. The humoral response to the BNT162b2 mRNA vaccine was enhanced in MS patients treated with IFN beta-1a sc according to a recent investigation in 150 subjects [181]: median anti-SARS-CoV-2 spike IgG titers were significantly higher in subjects receiving IFN beta-1a sc versus healthy volunteers and versus MS patients treated with cladribine, fingolimod, natalizumab, ocrelizumab or teriflunomide.

### 5.7. Risk of infection and disease severity of COVID-19

In a population-based study, MS patients were less likely to develop COVID-19 while being treated with IFN beta versus other MS DMTs ( $p < 0.001$ ), except for glatiramer acetate [182]. Moreover, the course of the disease may be more benign in patients with ongoing use of IFN beta [183]: the fatality rate of COVID-19 in patients receiving chronic treatment with IFN beta-1a sc appears to be relatively low versus external population-based comparator groups [184]. A large case-control study involving more than 2300 MS patients supported the notion that ongoing therapy with IFN beta is protective against the development of severe COVID-19 [185]. According to a network meta-analysis, IFN beta was the DMT associated with the lowest risk of severe COVID-19 [186]. In another meta-analysis, a higher proportion of patients being treated with IFN beta in a given cohort was significantly associated with lower COVID-19-related mortality ( $p < 0.001$ ) [187].

IFN beta appears to be critically involved in the physiological antiviral immune response to SARS-CoV-2 [188]. Cell culture experiments had already indicated in 2004 that IFN

beta-1a potentially inhibits the replication of SARS-CoV-1 [189]. Conversely, autoantibodies directed against type I IFNs [190,191] and lower IFN beta expression [192] were associated with substantially elevated vulnerability to COVID-19 infection. This finding may be of therapeutic interest as the viral spike proteins of some variant subtypes failed to induce endogenous IFN beta production [193]. Further research will elucidate the potential of IFN beta-1a sc in infectious diseases with an immune component amenable to cytokine-based interventions.

## 6. Conclusions

IFN beta-1a sc has accompanied patients with MS for the time span of a full human generation, and the drug continues to provide benefit for generations: from the first MS symptoms to SPMS, from young children to pregnant women and elderly adults with MS. The first successful therapeutic studies in patients with CIS and SPMS were conducted with IFN beta preparations, and recent studies on this therapeutic agent still deliver remarkable new insights. Based on extensive data from clinical studies and more recent *post hoc* analyses, IFN beta-1a sc remains a mainstay in the DMT of MS [16–18].

Treatment with IFN beta-1a sc delayed the disability progression in MS patients who were in apparent transition from RRMS to SPMS [81]. Thus, patients with both active disease and/or progressive worsening of disability may benefit from continued therapy with IFN beta-1a sc. If clinically required, treatment with IFN beta-1a sc may be considered individually during pregnancy [68,73], and the breastfeeding period [75], supporting its usefulness for female patients of the younger generation. Recent molecular investigations enabled the identification of additional players mediating the effects of IFN beta and of previously unrecognized biological effects that may contribute to beneficial therapy outcomes.

While more than 25 years of research and application underscore the usefulness of IFN beta-1a sc in one of the most prevalent chronic immune-mediated diseases, it is up to the current generation of researchers and physicians to further explore and fully exploit the potential of this pleiotropic immune regulator in autoimmunity and other areas of disease.

## 7. Expert opinion

IFN beta-1a sc has been used for two and a half decades as a first-line therapy in patients with MS. It is well established that IFN beta therapy reduces relapse rate, disability worsening, and lesion formation, thereby enhancing patients' quality of life. IFN beta-1a is therefore still frequently used in relapsing forms of MS, and it was shown to provide treatment benefits also for patients with SPMS who are still experiencing relapses. Moreover, IFN beta-1a may be useful as a de-escalation therapy once disease activity has been stabilized with another DMT. It is thus eligible for the treatment of MS patients with a wide range of ages, disease stages, and comorbidities – while real-world data on treatment efficacy in older patients remain limited.

The continued role for IFN beta-1a in clinical practice is further supported by the long history of favorable safety outcomes with comparatively mild side effects. Common side effects such as flu-like symptoms and injection site reactions are manageable through patient education and mitigation strategies. The safety profile in the pediatric MS population is similar to that in adults. Although a variety of DMTs with different risk-benefit profiles are now available, IFN beta-1a sc therefore continues to be the preferred choice for certain subpopulations of patients, including women who are planning to become pregnant as well as those breastfeeding. Advanced electronic devices for subcutaneous self-injection increase patient satisfaction and support adherence and cost-effective use of the medication.

Further research is needed to identify predictors of response to IFN beta therapy that may guide personalized treatment decisions for MS patients. Early intervention, i.e. starting in the period following CIS, is believed to be important for long-term beneficial outcomes. However, the mechanisms of waning efficacy in a subgroup of aging patients remain poorly understood. New technological developments, such as ultra-sensitive protein analyses, single-cell transcriptome sequencing, and metabolite profiling, may help to identify molecular biomarkers for predicting the clinical response to IFN-beta therapy. Advances in pharmacogenetics also offer the potential for more personalized treatment approaches in MS but still require thorough examination.

Research on the mechanisms of IFN beta provided valuable insights into the pathophysiology of MS that also informed the development of further treatments. IFN beta therapy alleviates disease progression by modulating both humoral and cellular immune responses, but we still lack a comprehensive knowledge of the diverse biological modes of action of endogenous and therapeutic IFN beta in MS. Additional investigations are required to better understand the involved signaling pathways and their cross-talks that modulate innate and adaptive immune responses and mediate neuroprotective effects by reducing the influx of pathogenic immune cells into the CNS.

IFN beta remains an important treatment option in MS for the foreseeable future, while the therapeutic landscape is constantly evolving. Studies of newer treatments for MS will continue to rely on IFN beta-1a sc as a reference for comparison. Further research efforts will be dedicated to the search for genetic, immunologic, environmental, and lifestyle factors that may influence the individual response to treatment. Advances in precision phenotyping and personalized medicine may hold promise for the future of IFN beta treatment in MS via the identification of patients with a higher likelihood of a substantial benefit.

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## Author contributions

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