

# Classical immunomodulatory therapy in multiple sclerosis

How it acts, how it works

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## ABSTRACT

Interferon beta (IFN $\beta$ ) and glatiramer acetate (GA) were the first immunomodulators approved to the treatment of relapsing-remitting multiple sclerosis (MS) and clinically isolated syndromes. Despite the enlargement of the therapeutic armamentarium, IFN $\beta$  and GA remain the most widely drugs and the therapeutic mainstay of MS. **Objective:** To review the mechanisms of action of IFN $\beta$  and GA and main clinical results in MS. **Results:** IFN $\beta$  modulates T and B-cell activity and has effects on the blood-brain barrier. The well proved mechanism of GA is an immune deviation by inducing expression of anti-inflammatory cytokines. Some authors favor the neuroprotective role of both molecules. Clinical trials showed a 30% reduction on the annualized relapse rate and of T2 lesions on magnetic resonance. **Conclusion:** Although the precise mechanisms how IFN $\beta$  and GA achieve their therapeutics effects remain unclear, these drugs have recognized beneficial effects and possess good safety and tolerability profiles. The large clinical experience in treating MS patients with these drugs along almost two decades deserves to be emphasized, at a time where the appearance of drugs with more selective mechanisms of action, but potentially less safer, pave the way to a better selection of the most appropriate individualized treatment.

**Key words:** multiple sclerosis, interferon beta, glatiramer acetate, immunomodulatory therapy.

## Terapêutica imunomoduladora clássica na esclerose múltipla: como atua, como funciona

## RESUMO

O interferon beta (IFN $\beta$ ) e o acetato de glatirâmero (GA) foram os primeiros imunomoduladores aprovados para o tratamento da esclerose múltipla (EM) surto-remissão e doentes com síndromes clinicamente isoladas. Apesar do alargamento do armamentário terapêutico, o IFN $\beta$  e o GA continuam a ser os medicamentos mais usados na EM. **Objetivo:** Rever os mecanismos de acção do IFN $\beta$  e do GA e os principais resultados na clínica. **Resultados:** O IFN $\beta$  modula a actividade das células T e B e tem efeitos sobre a barreira hemato-encefálica. O mecanismo melhor comprovado do GA é o desvio imune através da indução da expressão de citocinas. Alguns autores favorecem ainda um papel neuroprotetor para ambos. Os ensaios clínicos mostraram diminuição da taxa anualizada de surtos de 30% e das lesões em T2 na ressonância magnética. **Conclusão:** Embora os mecanismos pelos quais o IFN $\beta$  e o GA atingem os seus efeitos terapêuticos continuem a ser pouco claros, estes fármacos possuem efeitos benéficos reconhecidos e bons perfis de segurança e tolerabilidade. A grande experiência clínica no tratamento da EM com estes fármacos ao longo de quase duas décadas merece ser destacada, numa altura em que o aparecimento de novos fármacos com mecanismos de acção mais seletivos, mas potencialmente menos seguros, possibilitarão melhor seleção e individualização do tratamento.

**Palavras-chave:** esclerose múltipla, interferon beta, acetato de glatirâmero, terapêutica imunomoduladora.

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Multiple sclerosis (MS), the most frequent primary demyelinating pathology of the central nervous system (CNS), is a chronic and progressive autoimmune disease characterized by inflammation, demyelination and axonal injury<sup>1</sup>. The etiology of MS is ultimately unknown, although there is evidence that complex multifactorial factors are implicated, in which environmental are hypothesized to interact with genetically susceptible individuals<sup>2</sup>.

The clinical hallmarks of MS may be summarized as follows<sup>1</sup>: the disease typically begins in young adults and affects females more than males (1.77:1); most commonly, MS patients alternate relapses with remission phases (relapsing-remitting MS or RRMS), some of them developing later on a secondary progressive course (SPMS), and in a few cases, the disease progresses *ab initio* without (progressive MS or PPMS) or with rare superimposed relapses (transitional or progressive relapsing MS-RPMS); the disease is heterogeneous as regards neurological manifestations, evolution and disability; the diagnosis, based in international consensual criteria, depends strictly on clinical features and paraclinical exams, the most important of which is the magnetic resonance imaging (MRI); these criteria turned feasible the identification of patients with a clinically isolated demyelinating event or syndrome (CIS) that are at risk of conversion to a clinically definite disease (CDMS); finally, the progressive course and consequent neurological deficits inflict a significant disabling condition to the patient and a major burden to relatives, caregivers and society.

Although on the grounds of non-curative approaches, since the early nineties several pharmacological treatments with immunomodulatory properties were developed to treat MS and modify its natural history, commonly designated "disease modifying drugs" (DMD), which recognizably represented a major step in the control of the disease.

In this practical review we will focus on the classical immunomodulators specifically approved in MS - interferon beta (IFN $\beta$ ) and glatiramer acetate (GA) - highlighting their mechanisms of action (how they act) and their main clinical and imaging effects (how they work), based on the results of pivotal and comparative clinical trials. Despite the fast enlargement of the therapeutic armamentarium for MS in the last years, with the approval of drugs with better efficacy yet potential limiting adverse effects, as mitoxantrone and natalizumab (usually indicated in more severe non-IFN $\beta$ -responder cases), and the development of oral drugs, exemplified by the recently FDA approved fingolimod, IFN $\beta$  and GA remain up to now the worldwide therapeutic mainstay of MS.

### INTERFERON BETA

Interferons (IFNs) are proteins secreted by cells and

are involved in self defense to viral infections, in the regulation of cell growth and in the modulation of immune responses. Human IFN $\beta$  is a glycoprotein primarily produced by fibroblasts with 166 amino acids and 22.5 kDa, which is encoded on chromosome 9 without introns<sup>3</sup>. IFN $\beta$  was the first therapy to have proved beneficial effects on the natural course of MS and has two molecules: IFN $\beta$ -1a and -1b.

IFN $\beta$ -1a is obtained by eukaryote cell lines derived from a Chinese hamster ovary and, similarly to native human beta interferon, is glycosylated and has the complete 166 amino acid sequence; yet, the glycosylation pattern is not necessarily equal to the human<sup>3</sup>. IFN $\beta$ -1b is a product of a bacterial (*E. coli*) cell line and is not glycosylated because bacteria do not glycosylate proteins; additionally the cystein residue has been substituted by a serine at position 17, which prevents incorrect disulphide bond formation and minimizes the risk of impaired folding of the molecules and the consequent reduced activity; also, the methionine at position 1 has been deleted, so the final protein has one less amino acid than the natural IFN $\beta$ <sup>3</sup>. Glycosylation decreases aggregates formation and immunogenicity, which may give a lower potency of IFN $\beta$ -1a<sup>4</sup>, but, on the other side, IFN $\beta$ -1b has a tight binding to human serum albumin, which may contribute to about 10% of IFN $\beta$ -1a potency<sup>3</sup>.

### How it acts

IFN $\beta$  binds to a high-affinity type-1 IFN transmembrane receptors and induces a cascade of signaling pathways. After binding to the receptor, phosphorylation and activation of two cytoplasmic tyrosine kinases occur. This leads to activation of latent transcription factors in cell cytoplasm that translocate to the nucleus<sup>5</sup>. IFN $\beta$  has a role in the immune system by producing effects on T and B cells, and, additionally has influence in blood brain barrier (BBB) permeability<sup>6</sup>.

### EFFECTS ON T CELLS

**T cell activation** – IFN $\beta$  is believed to reduce T cells activation, including myelin reactive T cells, because interferes with antigen processing and presentation by downregulating expression of major histocompatibility complex (MHC) class II, and reduces the levels of costimulatory molecules<sup>7</sup> and other accessory molecules like intercellular cell adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), and very late activation antigen-4 (VLA-4)<sup>8</sup>.

**T cell differentiation and proliferation** – IFN $\beta$  inhibits the expansion of T cell clones, acting as an anti-proliferative agent. The exact mechanism for this anti-proliferative effect is unclear. Recently, it was demonstrated that type I IFNs, in which IFN $\beta$  is included,

could activate the Mnk/eIF4E kinase pathway that plays important roles in mRNA translation for IFN-stimulated genes and generation of IFN-inducible anti-proliferative responses<sup>9</sup>. Previous studies have indicated that Th17 cells have a critical role in the development of the autoimmune response in MS<sup>10</sup>. IFN $\beta$ -1a could induce an up-regulation of the TLR (toll-like receptors)-7 signaling pathway and inhibit multiple cytokines involved in Th17 cell differentiation. The authors propose that the exogenously administered high-dose IFN $\beta$ -1a augments this naturally occurring regulatory mechanism and provides a therapeutic effect in patients with RRMS<sup>11</sup>. Furthermore, IFN $\beta$  inhibits the expression of FLIP, an anti-apoptotic protein, leading to an increased incidence of T cells death<sup>12</sup> and restores T-regulatory cell activity<sup>6</sup>.

#### EFFECTS ON CYTOKINES AND CHEMOKINES

It has been postulated that the modulation of the immune response by IFN $\beta$  may involve an immune deviation, consisting in a reduction of the expression of Th1 induced cytokines while enhancing Th2 responses<sup>6</sup>. Additionally IFN $\beta$  has effects on chemokines: it could mediate activity of the chemokine receptor CCR7 which is important to direct the entry of T lymphocytes to the peripheral lymph nodes rather than to the CNS<sup>6</sup>. Another chemokine, Regulated on Activation, Normal T Expressed and Secreted (RANTES), appears to play a role in the pathogenesis of RRMS and was observed a decrease of its sera and peripheral blood adherent mononuclear cell levels triggered by IFN $\beta$ -1b<sup>13</sup>. A recent study suggested that peripheral upregulation of the chemokines by IFN $\beta$  may reduce the chemoattraction of immune cells to the CNS<sup>14</sup>.

#### ANTIGEN PRESENTATION

Furthermore, IFN $\beta$  is postulated to inhibit antigen presentation to T cells in conjunction with MHC and co-stimulatory molecules as CD80 and CD86, which is a crucial event in the ensuing immune response<sup>8</sup>. Another mechanism by which IFN $\beta$  can affect antigen presentation is by counteracting the effect of IFN $\gamma$ , because the latter cytokine is a potent promoter of MHC class II expression on many cell types<sup>8</sup>.

#### EFFECTS ON B CELLS

IFN $\beta$  upregulates a B-cell survival factor (BAAF) and for those patients in whom B cells play a major important role, this would be a quite undesirable consequence of IFN $\beta$  therapy. This might partially explain inter-individual differences in the therapeutic response. Otherwise, the systemic induction of BAFF by IFN $\beta$  therapy might facilitate the occurrence of various autoantibodies and IFN neutralizing antibodies (NAbs). The authors

conclude that individual MS patients with evidence for a significant role of B cells do not appear to be ideal candidates for IFN $\beta$  therapy<sup>15</sup>. However, B cells may trigger neurotrophic cytokines that exert positive effects on MS autoimmunity, which could outweigh the negative effects of IFN $\beta$ -induced BAAF responses<sup>6</sup>.

#### EFFECTS ON BBB

IFN $\beta$  is able to inhibit the ability of T cells to get into the brain by interfering with the expression of several molecules. It was demonstrated that matrix metalloproteinase type 9 (MMP-9) activity can be decreased by IFN $\beta$ -1b treatment *in vitro*<sup>16</sup>, which could difficult the migration of lymphocytes across the fibronectin of cerebral endothelium. Another study did not find any difference in the MMP-9 levels during the treatment with IFN $\beta$ <sup>17</sup>. Besides the role of the metalloproteinases, IFN $\beta$  can modulate the expression and traffic of other molecules like cytokines, chemokines, adhesion molecules and integrins<sup>16-18</sup>, improving endothelial barrier function and prevent the transmigration of leukocytes and other neurotoxic mediators across the BBB to sites of CNS inflammation<sup>10</sup>. One example is the possible induction of an increase in CD73 expression. Additionally, Uhm and colleagues found that the decrease in cell migration seems to wane with time as patients who have been receiving IFN $\beta$ -1b treatment for more than 3.5 years had high levels of T-cell migration that were indistinguishable from those of MS patients who have never been treated with IFN $\beta$ <sup>19</sup>. IFN $\beta$  may interfere with T-cell/endothelial cell adhesion by inhibiting MHC class II expression on endothelial cells, which can also function as ligands for T cells<sup>20</sup> and by decreasing the expression of VLA-4<sup>8</sup>. IFN $\beta$  also increases serum concentrations of soluble VCAM1 (sVCAM1), which might block leukocyte adhesion to activated cerebral endothelium by binding competitively with the VLA-4 receptor<sup>18</sup>. sVCAM1 had been correlated with a reduction in the number of MRI gadolinium-enhancing lesions soon after the initiation of treatment<sup>21</sup>.

#### ANTIVIRAL EFFECTS

Both formulations of IFN $\beta$  have antiviral properties, although IFN $\beta$ -1a seems to be more potent in this field<sup>6</sup>. A group of investigators studied the relation of MS-associated retrovirus (MSRV) in MS patients treated with IFN $\beta$ . They found that the viral load in the blood was directly related to MS duration and fell below detection limits within 3 months of IFN therapy, suggesting that evaluation of plasmatic MSRV could be considered a prognostic marker for the individual patient to monitor disease progression and therapy outcome<sup>22</sup>. Another group aimed to analyze IFN $\beta$  antiviral efficiency through the measurement of human herpesvirus-6 (HHV-6)

prevalence in MS patients and they noted a decreased number of reactivations of the virus associated with less relapses (42.8% of patients with viral reactivations experienced at least one relapse versus 22.5% of patients without viral reactivations)<sup>23</sup>.

#### NEUROPROTECTIVE EFFECTS

Some studies issued potential neuroprotective effects of IFN $\beta$ , inducing release of nerve growth factor from astrocytes or stimulate the protection of neurons themselves<sup>6</sup>.

Other investigators tried to measure the axonal injury *in vivo* using MRI spectroscopy to quantify the neuronal marker, N-acetylaspartate (NAA) and its relation with creatine (Cr) and found an increase in NAA/Cr in IFN $\beta$ -1b treated MS patients. Their data suggest that the axonal injury could be partially reversible with IFN $\beta$ -1b therapy<sup>24</sup>.

#### How it works

##### CLINICAL AND MRI OUTCOMES

The first multicenter, randomized and placebo-controlled study in RRMS patients with IFN $\beta$  was published in 1993<sup>25</sup>. This pivotal study demonstrated that IFN $\beta$ -1b 250  $\mu$ g subcutaneous (SC) produced a 34% reduction in the clinical relapse rate and in the confirmed 1-point EDSS progression rate after 2 years, better than a lower dose (50  $\mu$ g), yet the latter was not statistically significant compared with the placebo group<sup>25</sup>. Furthermore, the number and frequency of T2 active lesions on brain MRI were decreased<sup>26</sup>. Three years later, the results of a phase III trial with a similar design using IFN $\beta$ -1a 30  $\mu$ g/week intramuscular (IM) showed a 37% reduction in the confirmed 1-point EDSS progression rate. The median number of MRI-gadolinium enhancing lesions in MS was 33% inferior comparatively to the placebo arm. This pivotal trial also showed that IFN $\beta$ -1a slowed the accumulation of disability<sup>27</sup>. Since then, several trials confirmed these beneficial effects in RR form of MS<sup>28,29</sup> and in secondary progressive with relapses<sup>30</sup>. The patients with CIS who are considered with a high risk of CDMS have a proven benefit from early treatment with IFN $\beta$  to decrease clinical and MRI disease activity, as shown by specific studies conducted in CIS, either with IFN $\beta$ -1a<sup>31</sup> or with IFN $\beta$ -1b<sup>32</sup>.

As regards the route of administration, it does not seem to influence the biological effects of the IFN $\beta$  formulations<sup>33</sup>. Similarly, a dose-dependent effect remains a controversial issue. Although the pivotal trials suggested a dose-response curve, i.e., clinical and MRI outcomes seem to be better with higher doses, the evidence provided by them was considered somewhat equivocal<sup>34</sup>. However, other studies pointed out a trend to the same

result, in which higher dose and more frequently administered IFN $\beta$  was favored<sup>35,36</sup>, findings that were not corroborated by others<sup>37</sup>.

#### NEUTRALIZING ANTIBODIES (NABS)

During treatment with IFN $\beta$ , a proportion of MS patients develop NAbs. The potential impact of NAbs on the efficacy of IFN- $\beta$  treatment in MS is an area of debate and controversy, although their presence has been associated with a significant hampering of the treatment effect on the relapse rate and both active lesions and burden of disease in MRI. In Europe it is recommended that the patients treated with IFN $\beta$  are tested for the presence of NAbs at 12 and 24 months of therapy. In patients with NAbs, the measurement should be repeated at intervals of 3-6 months and if the titers continue elevated, IFN $\beta$  might be discontinued<sup>38</sup>. The American Academy of Neurology did not find enough evidence to make specific recommendations about when to test, which test to use, how many tests are necessary, and which cutoff titer to apply<sup>39</sup>.

#### Side effects

Therapy with IFN $\beta$  is usually well tolerated. The most frequent side effects are flu-like symptoms and injection-site reaction, which tend to reduce over time. Depression, allergic reaction, haematologic and liver function abnormalities might also be observed<sup>40</sup>. IFN $\beta$  is a safe treatment, but usually is not recommended during pregnancy because of the higher risk of fetal loss and low birth weight<sup>41</sup>.

#### IFN formulations and indications

The actual commercially available formulations of IFN $\beta$  include IFN $\beta$ -1a and IFN $\beta$ -1b. IFN $\beta$ -1a is dosed in 30  $\mu$ g (Avonex<sup>®</sup>), 22 or 44  $\mu$ g (Rebif<sup>®</sup>). The first is applied once a week by IM and the second three times a week with a SC injection. IFN $\beta$ -1b formulations have 250  $\mu$ g (Betaferon<sup>®</sup> or Betaseron<sup>®</sup>, and Extavia<sup>®</sup>) and are administered by SC injection every other day. All formulations are indicated in RRMS, IFN $\beta$ -1a IM and IFN $\beta$ -1b are also approved in patients with CIS at risk of conversion to CDMS and IFN $\beta$ -1b is furthermore approved in Europe to treat patients with SPMS still with relapses.

#### GLATIRAMER ACETATE

Glatiramer acetate is a synthetic polypeptide composed of four amino acids (L- glutamic acid, L- lysine, L- alanine and L- tyrosine) with an average molecular mass of 4700-11.000 Da. It was discovered in the 1960's, when studies to develop a polymer resembling myelin basic protein (MBP), a major component of myelin sheath, to the model of autoimmune encephalomyelitis (EAE), were

performed<sup>42</sup>. One of them, called copolymer 1, demonstrated to decrease or prevent EAE, and was later renamed as GA<sup>43</sup>.

#### How it acts

Several mechanisms of action have been proposed, yet the precise biological effects of GA are not fully understood. We present the main effects on T and B lymphocytes and on antigen presenting cells (APCs).

#### EFFECTS ON T CELLS

**Inhibition of myelin reactive T cells and immune deviation** – GA binds directly to MHC class II, but also seems to be able to interact with MHC class I<sup>44</sup>. GA interferes with the activation of myelin-specific T cells based on the observation that it acts as an antagonist to MBP/MHC at MBP-specific T cell receptor (TCR), operating as an altered peptide ligand to the 82-100 epitope of MBP *in vitro*<sup>42</sup>, displacing MBP from the binding site on MHC II molecules. Some authors argued that this “TCR antagonism” is controversial and, whether it occurs, is not probably relevant *in vivo* because GA is unlikely to reach sites where it could compete with MBP. However, GA-reactive Th2 cells are able to cross the BBB and might be activated not only by MBP, but also by other cross-reactive antigens<sup>44</sup>. Myelin reactive T cells exposed to increasing doses of GA manifest dose-dependent inhibition of proliferation and IFN $\gamma$  production. That proliferative response of T cells to GA decreases with time. In addition, the observed decrease in GA-reactive T cells could be caused by the induction of T cell energy and clonal elimination<sup>45</sup>. This mechanism of T cell energy can occur in the periphery at the injections sites or in their draining lymph nodes where the MBP specific cells might be confronted with GA. The used regimen of daily SC administration may favor the induction of anergy rather than a full immunization that requires longer intervals between doses<sup>46</sup>. However, some clonal populations of T cells could be expanded, since GA induced the conversion of peripheral CD4+CD25– to CD4+CD25+ regulatory T cells through the activation of transcription factor Foxp3 and lead to proliferation of these cells. However, this fact must be interpreted with caution because almost all activated human T cells express Foxp3<sup>42</sup>. Therapy with GA may improve the immune regulatory function of CD8+ T cells<sup>42</sup>. These data suggest that the immunomodulatory effect of GA is attributed to the induction of a cytokine secretion pattern deviation from Th1 to Th2 cytokines, as happens with IFN $\beta$ <sup>43</sup>, which is the mechanism with the strongest experimental support.

#### BYSTANDER SUPPRESSION

Another potential mechanism of action is the so

called bystander suppression: a phenomenon of T cells specific to one antigen which suppress the immunological response induced by another antigen<sup>46</sup>. This implies that GA-reactive Th2 cells are capable of entering the CNS and recognizing cross-reactive antigen(s), probably myelin antigen(s)<sup>44</sup>. It is characterized by the secretion of anti-inflammatory cytokines by GA-activated T cells after they cross the BBB and accumulate in the CNS<sup>43</sup>.

#### EFFECTS ON CELL-PRESENTING ANTIGENS

Although the vast majority of evidence suggests that GA acts primarily at the level of T cells, additional effects on other immune cells cannot be excluded. For example, GA was reported to inhibit a human monocytic cell line, THP-1. In THP-1 cells stimulated with lipopolysaccharide or IFN- $\gamma$ , GA reduced the percentage of cells expressing MHC-DR and DQ antigen and inhibited the production of TNF- $\alpha$  and cathepsin-B. In contrast, the production of interleukin(IL)-1 $\beta$  was increased<sup>47</sup>. This could also indicate antigen-unspecific modes of action. A further study also demonstrated that GA affects monocytes/macrophages by inducing the production of an anti-inflammatory cytokine, the IL-1 receptor antagonist (IL-1Ra), but diminishing the production of IL-1 $\beta$  in monocytes, activated by direct contact with stimulated T cells in MS patients and in the EAE model<sup>48</sup>. IL-1Ra can be transported through the BBB and exert its immunomodulatory effects in both systemic and CNS compartments. In addition to the modulation of the adaptive immune system, GA seems to affect significantly the innate immune system<sup>48</sup>.

GA may also affect the immune response through modifying APCs into anti-inflammatory type II cells. The process begins with the presentation of GA to CD8+ and CD4+ T cells by APCs. The final step is an alteration of cytokine environment that subsequently affect T-cell differentiation as far as concerned to further cytokine secretion. The T cell CD8+ response becomes oligoclonal with expansion and maintenance of CD8+ clone population over long periods of time, in contrast to what happens to T cells CD4+ which may increase in number<sup>42</sup>.

#### NEUROPROTECTIVE EFFECTS

Furthermore, GA specific T cells secrete neurotrophic factors as brain-derived neurotrophic factor and neurotrophic growth factor, which might favor remyelination and axonal protection<sup>42,43,49</sup>. A study with MRI spectroscopy showed a significant increase in NAA/Cr in a group of treatment naive patients with RRMS, who received GA compared with untreated patients, suggesting the potential role of GA in axonal metabolic recovery and protection from sublethal injury<sup>50</sup>. Another potential effect of GA is the delivery of neuroprotective cytokines

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