

## PHARMACOLOGICAL TREATMENT OF RELAPSING REMITTING MULTIPLE SCLEROSIS-WHERE ARE WE?

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### Abstract

Multiple sclerosis is a chronic disease of the central nervous system, characterized by inflammation, demyelination and neurodegeneration. The cause of the disease is not known, but the mechanism is assumed to be an auto-immune one. For the disease occurrence, two conditions are necessary: genetic predisposition and certain environmental factors acting as activating factors. The total costs of this disease are high, as it affects mainly young people aged 20 - 40, the evolution is long, requiring medical care, expensive treatments, recovery, in parallel with the loss of productivity at a certain moment, during the disease evolution. Thus, the interest for an efficient, affordable and safe medication is of high interest. Today, we have two categories of drugs modifying the evolution of this diseases as well as guides of diagnosis and treatment that are periodically changing, according to the results of the clinical studies and of evidence-based medicine. As such, we aimed at pointing out the main approved to treat the relapsing-remitting form of multiple sclerosis (RRMS).

### Rezumat

Scleroza multiplă este o afecțiune cronică a sistemului nervos central, caracterizată prin inflamație, demielinizare și degenerescență. Cauza bolii nu se cunoaște, dar mecanismul se presupune a fi unul autoimun. Pentru ca boala să apară sunt necesare două condiții: predispoziția genetică și anumiți factori de mediu care să acționeze ca factori declanșatori. Costurile totale ale bolii sunt mari, deoarece afectează în principal tinerii între 20 - 40 ani, evoluția este lungă, necesitând îngrijiri medicale cu tratamente costisitoare, recuperare, în paralel cu pierderea productivității, la un moment dat, în evoluție. Astfel, interesul pentru o medicație eficientă, ieftină, sigură, este maxim. Dispunem astăzi de două categorii de medicamente care modifică evoluția bolii și de ghiduri de diagnostic și tratament, care se actualizează periodic, în funcție de rezultatele studiilor clinice și a medicinei bazate pe dovezi. Prin prisma acesteia, ne-am propus să trecem în revistă principalele medicamente care au fost aprobate pentru tratamentul formei remisiv recurente a sclerozei multiple.

**Keywords:** remitting form of multiple sclerosis (RRMS), disease-modifying therapies (DMTs), MoAbs, Cochrane Reviews

### Introduction

Multiple sclerosis is a chronic disease of the central nervous system (CNS), characterized by episodes of inflammation and focal demyelination, with multiple localizations disseminated in time, for a person who is genetically prone to develop the disease. Multiple sclerosis is most probably based on auto-immune mechanisms directed against myelin proteins, mediated by T lymphocytes and activated by exogenic factors. It associated a process of axonal degeneration and an abnormal oligodendrocyte function, carried out in parallel, with a progressive evolution [1]. Therefore, beside demyelination, there are alterations specific to neurodegenerative diseases, with axonal dysfunctions and atrophy, but also heterogenic inflammatory processes [2].

The Romanian researcher Gheorghe Marinescu (1863 - 1938), collaborator of Charcot and of Santiago Ramón y Cajal, supported the viral origin of this disease, considering that the destruction of the myelin sheath of neurons is caused by the myelinolytic lipase, contained by the pathogenic virus [3]. The genetic predisposition for this disease is amplified by environmental factors such as viruses, chemical agents, smoking, obesity or the level of vitamin D [4].

Probably one of the first documented cases of multiple sclerosis is that of the Dutch Saint Lidwina of Schiedam (1380 - 1433), whose disease had its onset when she was 18 years old and which progressed slowly, causing her death at the age of 53. Another more recent case and better documented is that of Augustus d'Este (1794 - 1848), son of the

duke of Sussex and cousin of Queen Victoria, who kept, for 22 years, a very thorough journal of his disease [5].

The social cost of the disease is higher than that of Alzheimer's dementia or the costs related to stroke, as it affects mostly young people between 20 - 40 years old, who develop a physical disability determining the loss of productivity, requiring care, expensive treatments, recovery, provided by multidisciplinary teams, for a long time, the disease evolving progressively and affecting the quality of life (QoL).

The total average cost for a patient suffering from multiple sclerosis, in 2007, was approximated to 41,000 U.S. dollars, with variations according to the costs and type of local medical care (16,400 U.S. dollars for France and 54,500 U.S. dollars for Sweden and Norway) [7].

Until the 1950s, various treatments for this disease have been assessed, such as anti-infectious, anti-inflammatory, anti-allergic, vasodilator drugs, vitamins, psychiatric drugs, physical therapies, without promising results. In 1969, using the diagnosis criteria of the disease and the accurate scientific methods represented by clinical controlled trials, the efficiency of a treatment for this disease was proven for the first time, namely that of ACTH (Adrenocorticotrophic Hormone). Beginning with the 1980s, by magnetic resonance imaging (MRI) techniques and controlled clinical studies, copolymers and interferons were studied, that are subsequently introduced in the treatment of the disease, because they reduce the rate of relapses and delay the conversion from CIS (clinically isolated syndrome) to CDMS (clinically definite multiple sclerosis), with a modest effect on the progression of the disease. Thus, these new molecules were called DMTs (disease-modifying therapies) [8].

### Disease-modifying therapies (DMTs)

#### *First line treatment for RRMS*

The multitude of drugs currently used to treat MS is divided into two categories: *first line drugs*, with moderate efficiency and a better long-term safety profile (mainly for IFNs and GA): IFNs (Avonex<sup>®</sup>, Betaferon<sup>®</sup>/Betaseron<sup>®</sup>/Extavia<sup>®</sup>, Rebif<sup>®</sup>, Plegridy<sup>®</sup>), GA-glatiramer acetate (Copaxone<sup>®</sup>/Glatopa<sup>®</sup>), teriflunomide (Aubagio<sup>®</sup>), dimethyl fumarate (Tecfidera<sup>®</sup>); *second line drugs*, with greater efficiency, but lesser safety: fingolimod (Gilenia<sup>®</sup>, Gilenya<sup>®</sup>), natalizumab (Tysabri<sup>®</sup>), alemtuzumab (Campath<sup>®</sup>, MabCampath<sup>®</sup>, Lemtrada<sup>®</sup>) [9,10,11].

The interferon  $\beta$ -1b (IFN  $\beta$ -1b) – Betaseron<sup>®</sup>/Betaferon<sup>®</sup> was the first DMT approved in 1995 by European Medicines Agency (EMA) for RRMS treatment. In 1996, there was approved the Interferon  $\beta$ -1a (IFN  $\beta$ -1a) – Avonex<sup>®</sup>, in 1998

Interferon  $\beta$ -1a (IFN  $\beta$ -1a) – Rebif<sup>®</sup> and in 2001 Glatiramer acetate – Copaxone<sup>®</sup> [12]. In 2014, it was approved Peginterferon beta-1a (Plegridy<sup>®</sup>) that has a longer action than Avonex<sup>®</sup> [10].

Interferons are proteins produced in very small quantities by animal or human cells, when a virus enters the body. Through techniques of genetic engineering, using ovarian hamster cells or *Escherichia Coli* cells, these synthetic interferons were obtained, to treat MS. The glatiramer acetate is a copolymer formed of four amino acids existing in the myelin basic protein. The treatment is injectable, and the frequency of intramuscular (Avonex<sup>®</sup>) or subcutaneous administration (for the other preparations) varies from daily to once a week, according to the drug.

The local adverse reactions consist in erythema, pain, cutaneous necrosis, lipoatrophy. The systemic reactions are flu-like symptoms, leukopenia, elevation of liver enzymes, increase of spasticity, depression and very rarely anaphylactic reactions or systemic post-injection reaction [13].

The short-term and long-term safety profile has proven to be very good, the risk/benefit ratio being an appropriate one. Cochrane systematic studies based on five Randomised Controlled Trials (RCTs) lasting for 2 or 3 years, aimed precisely at emphasizing the safety and efficiency of the treatment by IFNs and GA for patients with RRMS. The conclusions published in 2014 were that both IFN and GA had similar effects in patients with RRMS, from the clinical point of view (the rate of relapses and progression of the disease), but different in terms of magnetic resonance imaging (MRI), the reduction of the volume of cerebral lesions being higher in the group treated by IFNs compared to GA [14].

The current treatment guidelines recommend, therefore, IFNs and GA as first-line medication for the clinical isolated syndrome (CIS) and the remissive-recurrent forms of MS, immediately after correctly diagnosing the disease, IFNs being also recommended in the forms of secondary progressive disease with relapses.

Recently, there were added two other molecules to this first line of treatment: teriflunomide and dimethyl fumarate.

*Teriflunomide*, was approved in Europe in 2013 to treat RRMS in a dose of 14 mg/day [15, 16]. Aubagio<sup>®</sup> (the marketed name), inhibits proliferating lymphocytes by blocking dihydroorotate-dehydrogenase. Among the adverse reactions, are to be noted: alopecia, nausea, diarrhoea, hepatotoxicity, leukopenia, polyneuropathies, renal insufficiency, arterial hypertension, pancreatic fibrosis, infections. A Cochrane review published in 2016 assessed 5 studies with 3231 patients. It found poor evidence supporting the effect of teriflunomide in a dose of 7 or 14

mg/day as monotherapy, in reducing relapse rate after one or two years of treatment, compared to *placebo*. The adverse effects were easy and moderate as severity, with dose-related effect [17]. Another immune-modulator, *dimethyl fumarate*, used for the treatment of psoriasis, was approved in 2014 by EMA for the oral treatment of RRMS under the commercial name of Tecfidera<sup>®</sup>, 240 mg twice a day. The exact mechanism of action is unknown, like for most existing products treating DMTs. The adverse reactions include lymphopenia in 30% of the cases, especially in the first year of treatment, partially reversible, face erythema in up to 40 % of the cases, nausea, abdominal pain, diarrhoea, dyspepsia, progressive multifocal leukoencephalopathy (PML) [18]. Two RCTs with 2667 patients with RRMS were assessed in terms of efficiency and safety of dimethyl fumarate in doses of 240 mg, twice or three times a day, compared to *placebo*, for two years. The conclusions published in 2015 claimed that there is moderate-quality evidence to reduce the rate of relapses as compared to *placebo*. Both doses had similar safety benefits and profiles, thus recommending using the smaller one [19].

#### *Second line treatment for RRMS*

IFNs and GA have no effect or suboptimal effect concerning the disease progression, approximately 33% of the treated patients gave up their treatment because they did not see their real benefit. In these cases, it is recommended to change the medicine with one of the first line, or to start using another 2<sup>nd</sup> line drug [20].

Since 1974, when the first monoclonal antibody was marketed, a new era has started in the therapy of dermatologic (efalizumab, ustekinumab), rheumatic (tocilizumab, adalimumab, golimumab), gastroenterological (infliximab, certolizumab), neoplastic (alemtuzumab, rituximab, ofatumumab, bevacizumab) diseases or of organ transplants (daclizumab, basiliximab). The monoclonal anti-bodies (MoAbs) are monovalent antibodies that bind to the same epitope and which are produced by one single clone of B lymphocytes.

*Natalizumab* (Tysabri<sup>®</sup>) was the first monoclonal antibody used to treat a neurological disease [21, 22]. It was approved for patients with a very active RRMS, according to certain clinical and imaging criteria, in 2006, by EMA. The main action is to prevent lymphocytes from crossing blood-brain barrier, by blocking adhesion molecules. It is administrated in i.v. perfusion in a dose of 300 mg every 4 weeks. As adverse reactions, the increase of liver enzymes, hypersensitivity or infections by John Cunningham virus (JCV), that are deadly in 20% of the cases and has cumulative risks in time, have been identified [23, 24]. Thus, it is indicated to stratify the risk based on several factors: the

presence of anti JCV – antibodies, prior treatments with immunosuppressant and over 2 years natalizumab treatment.

In 2011, EMA approved the first drug with oral administration to treat highly-active RRMS,  *fingolimod* (Gylenia<sup>®</sup>). In the dose of 0.5 mg daily, it reduces the relapses rate by 54%, the cerebral lesions by 67%, by modulation sphingosine-1-phosphate receptors. The adverse reactions are mainly cardiac (1-10%): cardiac insufficiency, atrial-ventricular (AV) blocks, but also macular oedema, cutaneous cancer, encephalitis, increase of liver enzymes, fever, diarrhoea, hepatotoxicity and rare PML [25].

A Cochrane study, on six RCTs and 5152 participants, published in 2016, aimed at analysing the safety and efficiency of fingolimod *versus placebo* or other DMTs. The conclusions were that fingolimod is efficient in decreasing the relapses rate as compared to *placebo*, but it could not be proven that it would prevent the disability progression. Also, the risks of the treatment require careful monitoring (EKG, liver function monitoring, eye and heart detailed examination), and even interrupting treatment if the situation requires it [26]. It is not recommended to perform vaccination with live attenuated viruses during therapy by fingolimod and nor two months after the treatment stops.

*Alemtuzumab* (Campath<sup>®</sup>, Lemtrada<sup>®</sup>), discovered in the pathology laboratory of Cambridge University, which gave its name – Campath<sup>®</sup> – is used for patients suffering from chronic lymphocyte leukaemia, that do not respond to fludarabins. It also received approval for the treatment of RRMS in Europe, in 2013, being the second monoclonal anti-body, after natalizumab, for the treatment of MS. The mechanism of action is the long-term depletion of lymphocytes CD52. The recommended dose is 12 mg daily for 5 consecutive days, with another dose of 12 mg/day 3 consecutive days administrated by infusion after one year [27]. Despite the adverse reactions, as auto-immune diseases occurrence or local reactions to the perfusion site, it is a drug used in the active forms of the disease. A short administration of corticosteroids before each infusion together with antihistamines, antipyretics and antivirals may be beneficial in order to reduce these adverse reactions.

The authors of a Cochrane review of 2016 show that, for patients suffering from RRMS, alemtuzumab 12 mg was better than IFN-beta-1a after 24 months, regarding the absence of relapses, progression of the disease, adverse reactions or MRI lesions [28].

A Cochrane meta-analysis of 2015 had as main objective the comparison between the benefit of interferon beta-1b, interferon beta-1a, glatiramer acetate, natalizumab, mitoxantrone, fingolimod,

teriflunomide, dimethyl fumarate, alemtuzumab, pegylated interferon beta-1a, daclizumab, laquinimod, azathioprine and immunoglobulins in the treatment of patients suffering from RRMS, referring to the treatment interruption rate due to adverse reactions. 39 studies with 25,113 participants were included with the average follow-up duration of 24 months. The conclusions were that alemtuzumab, natalizumab, fingolimod are the best choices for RRMS in the first 24 months, but to prevent the aggravation of the disability, only natalizumab was efficient. However, these aspects are irrelevant, because the follow-up term was low, 24 months compared to the length of the disease, of 30 - 40 years [29]. Other monoclonal anti-bodies are in various stages of investigation for the treatment of RRMS: laquinimod, rituximab, ocrelizumab, ofatumumab and daclizumab.

### Practical considerations

All drugs approved for RRMS treatment reduce the relapse rate and the increase of cerebral lesions shown by MRI, at a certain extent [30].

The  $\beta$ -interferons, glatiramer, teriflunomide, dimethyl fumarate reduce the relapses rate by 30 - 50%, as they are considered moderately efficient drugs. On the other hand, alemtuzumab and natalizumab are considered to be highly efficient, reducing the relapses rate by over 50% [12, 31].

Disease-modifying treatment is not indicated in the progressive forms of multiple sclerosis, due to its lack of efficiency. Clinicians still cannot specify how many relapses should be encountered in order to pass the patient from being treated by a first-line drug to a second-line drug; more clinical studies are required for these purposes.

New MRI lesions are much more sensitive to appraise the activity of the disease than relapses rate, being 10 times more frequent [32]. This is the reason why the European Medicines Agency admits that the "activity" of the disease should be appreciated both clinically and radiologically.

Immune therapies are beneficial in the very active forms of RRMS, administrated early, before the onset of the disability. The therapy is changed when the patient fails to answer the initial treatment. The induction therapy implies the administration of a potent drug, usually with important adverse reactions [33]. There are needed clinical studies for these purposes, showing the benefits and risks of these treatment strategies.

As in Parkinson disease, the non-motor problems in MS are of great importance. Unfortunately, DMTs have unknown effects on fatigue, anxiety, depression, pain, cognitive disorders, sphincter dysfunctions [34]. If for Alzheimer disease we have effective treatments, research studies on the

treatment for cognitive impairment in MS patients are ongoing [35, 36].

Patients suffering from RRMS will begin their treatment with a first-line drug, fingolimod and dimethyl fumarate being the most active ones in this category, having the great advantage of the oral administration. IFNs and GA are somewhat less efficient, but they passed the test of time, showing a good safety profile.

For the very active forms of the disease, under treatment with GA and IFN, a second-line drug starts being prescribed, natalizumab or alemtuzumab.

### Conclusions

The DMT is partially efficient and not curative, with risks and benefits, it requires chronic administration and careful monitoring, and the individual response is unpredictable. Moreover, most forms of multiple sclerosis are remissive and recurrent on the onset, and later they turn progressive, and no treatment has proven to be efficient, so far. On the other hand, there are benign forms of the disease even, in the absence of treatment. Currently, there are more and more research studies investigating the etiopathogenicity of the disease and an individualized, personalized, efficient treatment, with a good long-term safety profile and with affordable prices.

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