



## Clinical advances in multiple sclerosis and amyotrophic lateral sclerosis treatment: A review

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<https://doi.org/10.36105/psrua.2021v1n2.06>

### ABSTRACT

Neurodegenerative diseases are clinical manifestations that depend on the anatomy and function of the affected areas. Amyotrophic lateral sclerosis (ALS) and multiple sclerosis (MS) are some of these diseases, but they are also autoimmune and their etiology makes treatments limited and of little therapeutic efficacy. Currently, some clinical research advances can be pillars for the development of new treatments for these diseases. Therefore, the objective of this review is to describe the latest clinical advances in ALS and MS as well as their results in clinical recovery in randomized clinical trials, meta-analyzes, and full-text systematic reviews conducted in humans and rats, published in English and Spanish in the last 5 years, using PubMed, SciELO, and Cochrane. For clinical trials to be included, they had to provide a detailed breakdown of randomization methods, diagnostic criteria, intervention details, and efficacy evaluation. The results show that, so far, available medications, like riluzole and edaravone for ALS and fingolimod, dimethyl fumarate, and IFN  $\beta$ -1b for MS, only prolong the life of the patient. Among these drugs are also glutamate neurotransmitter antagonists, immunomodulators and even antioxidants; each of them showed significant improvement in the reviewed trials. Similarly, other non-pharmaceutical treatments, as the 600-mg dose of curcumin in the diet for ALS, showed improvement of the patients' conditions. Regarding MS, more studies should be carried out on autotransplantation with adipose-derived mesenchymal stem cells (AdMSCs) to investigate the potential therapeutic benefit of this technique in phases prior to secondary-progressive (SPMS).

**Key words:** clinical advances; treatment and multiple/amyotrophic lateral sclerosis; sclerosis.

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## RESUMEN

Las enfermedades neurodegenerativas son manifestaciones clínicas que dependen de la anatomía y función de las zonas afectadas. La esclerosis lateral amiotrófica (ELA) y la esclerosis múltiple (EM) son algunas de estas enfermedades, además, son autoinmunes y su etiología hace que los tratamientos sean limitados y de escasa eficacia terapéutica. Actualmente, algunos avances en la investigación clínica de estas enfermedades pueden ser pilares para el desarrollo de nuevos tratamientos. Por tanto, el objetivo de esta revisión es describir los últimos avances clínicos en ELA y EM, así como los resultados de recuperación clínica en ensayos clínicos aleatorios, metanálisis y revisiones sistemáticas de textos completos realizados en humanos y ratas, publicados en inglés y español en los últimos 5 años mediante PubMed, SciELO y Cochrane. Para ser incluidos, los ensayos clínicos debieron proporcionar un desglose detallado de los métodos de aleatorización, los criterios de diagnóstico, los detalles de las intervenciones y la evaluación de la eficacia. Los resultados muestran que hasta ahora solo existen medicamentos que prolongan la vida del paciente, riluzol y edaravona para ELA y fingolimod, dimetilfumarato e IFN  $\beta$ -1b para EM, principalmente. Entre estos medicamentos se encontraron también antagonistas del neurotransmisor glutamato, inmonomoduladores e incluso antioxidantes; cada uno de ellos mostró una mejoría significativa en los ensayos revisados. De igual forma, otros tratamientos no farmacéuticos demostraron mejoría de los pacientes con dichas enfermedades, como la dosis de 600 mg de cúrcuma en la dieta de los pacientes con ELA. En cuanto a EM, se deben realizar más estudios sobre el autotrasplante con células madre derivadas de tejido adiposo mesenquimatoso (AdMSC) para investigar el beneficio terapéutico potencial de esta técnica en fases previas a la esclerosis múltiple secundaria progresiva (SPMS por sus siglas en inglés).

**Palabras clave:** avances clínicos; tratamiento y esclerosis múltiple/esclerosis lateral amiotrófica; esclerosis.

## INTRODUCTION

Neurodegenerative diseases are those clinical features that depend on the anatomy and function of the affected areas. As they progress, they produce atrophy in the damaged areas of the cortex, which can be detected in imaging studies or macroscopic examinations of the brain. Histologically, they are characterized by gliosis and neuronal loss by apoptosis. In some cases, the activation of the microglia is observed, suggesting that a low-grade inflammatory mechanism contributes to the diseases. Some of these diseases have well-defined genetic alterations, but others are sporadic. The latter currently constitute a primary field in biomedical research due to the lack of effective treatments to stop their progress and the failure of treatments to allow the patients' recovery.<sup>1,2</sup>

There are several subclassifications of neurodegenerative diseases, one of which is autoimmune in nature. Autoimmunity refers to the presence of autoantibodies or T lymphocytes that react against autoantigens, and it does not necessarily imply that the appearance of self-reactivity has pathological consequences. Autoimmunity is found in all people and increases with age; however, autoimmune diseases arise only when the transgression of one or more of the basic mechanisms regulating immune tolerance leads to self-reactivity and, therefore, to tissue damage.<sup>2</sup> Amyotrophic lateral sclerosis (ALS) and multiple sclerosis (MS) are two autoimmune neurodegenerative diseases. But compared to other neurodegenerative diseases, just a few therapeutic strategies have been developed to treat them since their etiology makes treatments limited and with

little therapeutic efficacy. Some advances in clinical research can be pillars for the development of new treatments for these diseases. The objective of this study was to describe the latest clinical advances in ALS and MS as well as the results of clinical recovery in randomized clinical trials, meta-analyses, and full-text systematic reviews conducted in humans and rats published in English and Spanish in the last 5 years using PubMed, SciELO, and Cochrane.

## AMYOTROPHIC LATERAL SCLEROSIS

ALS is a neurodegenerative disease characterized by a primary degeneration of motor neurons that causes weakness and atrophy of the affected muscles. It is the most common motor neuron disease and is characterized by the degeneration of both upper and lower motor neurons.<sup>3</sup> From a macroscopic point of view, the ALS brain appears normal, although atrophy of the precentral gyrus is sometimes observed; the spinal cord is thinned, and the anterior motor roots are atrophic and gray in color, as compared to the posterior ones, which are sensitive. Histologically, the main alteration in ALS is the loss of motor neurons with gliosis in the anterior horn of the spinal cord, stem, and motor cortex. Seen in the surviving motor neurons, Bunina bodies are eosinophilic inclusions, 2–5  $\mu$  in diameter in the cell body, reactive for ubiquitin. The white matter of the spinal cord shows pallor of the corticospinal tracts.<sup>2</sup> The clinical picture is characterized by the onset of muscle twitching and weakness of one limb (usually upper) that then spreads to other parts of the body. As the disease

progresses and nerve cells are destroyed, muscles weaken. This eventually affects chewing, swallowing, speaking, and breathing. Eventually, ALS affects the control of the muscles needed to move, speak, eat, and breathe. There is no cure for this disease and there is no involvement of the sensory part or bladder dysfunction as in myelopathies, which is the first differential diagnosis. Risk factors for developing ALS are smoking; hereditary factor (5–10% patients inherit Familial Lateral Amyotrophic Sclerosis), exposure to environmental toxins, sex (it has been shown that male sex present higher prevalence), and age (40–65 years).<sup>4</sup>

### Pathophysiology

The disease process is virtually limited to the motor neurons of the cerebral cortex, brainstem, and spinal cord, and certain forms of progressive ataxia affecting only the Purkinje cells of the cerebellum. It is based on neuron exhaustion and loss: Not only do the cell bodies disappear but also their dendrites, axons, and myelin sheaths, a phenomenon that is not accompanied by an intense tissue or cellular response. The cerebrospinal fluid (CSF) shows little if any change in protein content.<sup>5</sup> Several processes at cellular level characterize the death of individual cells. The pathological neuronal degeneration process is very different because it refers to a series of changes in mature neurons that occurs over an extended period, leads to cell death, and usually leaves a discrete glial scar but not regional tissue necrosis. In many models of degenerative disease, cell loss encompasses the activation of specialized genes, although their chronological evolution and cell morphology are not apoptotic. It has become clearer that mechanisms other than programmed cell death are essential for understanding degenerative diseases and that the clinical manifestations of such disorders occur even before cell destruction. For example, interference with synapse signaling and supporting glial cell dysfunction is as important as morphological neuronal death.<sup>5</sup>

### Conventional clinical treatments

ALS is the most common motor neuron disease in adults, and no effective treatment is currently available beyond supportive care with some moderately life-prolonging supportive medications. Among these drugs is riluzole; it is absorbed orally and metabolized in the liver by cytochrome P450 (CYP)-mediated hydroxylation and glucuronidation. It has presynaptic and postsynaptic effects as it not only inhibits glutamate release but also blocks postsynaptic glutamate receptors like NMDA (N-methyl-D-aspartate) and kainate and inhibits voltage-gated Na<sup>+</sup> channels. The recommended dose is 50 mg twice a day, taken one hour before or two hours after a meal. It is generally well tolerated but can eventually cause nausea or diarrhea. Although the magnitude of its effect in ALS is small,

riluzole represents a significant therapeutic milestone in the treatment of a disease refractory to all previous treatments.<sup>3,7</sup> Another drug used in the treatment of ALS is edaravone, a small molecule with free radical-scavenging properties that can reduce oxidative stress. It has been used in Japan for acute strokes since 2001 and was approved by the FDA for ALS under an orphan drug designation. The treatment is given in cycles, the first one is given intravenously daily for 14 days, followed by a 14-day break, then in subsequent cycles, 10 out of 14 days followed by a 14-day break. The drug is metabolized to glucuronide and sulfate and is excreted mainly in the urine as glucuronide, producing a terminal t<sub>1/2</sub> of 4.5–6 h.<sup>3</sup>

### MULTIPLE SCLEROSIS

MS or plaque sclerosis is a chronic neurological inflammatory and autoimmune disease characterized by demyelinating lesions and axonal damage in the central nervous system (CNS) that cause disability. It affects 1 in 1000 people, especially women (2:1 ratio compared to men). It generally affects people from 16–55 years old. The race most affected is white, of northern European descent. It begins with the appearance of focal inflammatory lesions in the cerebral white matter and a demyelination of neurons. Axons are preserved in the early phase of the disease, but the disease can cause deterioration or permanent damage to the nerves over time. Myelin is a lipoprotein structure that isolates axons, facilitating smooth and high-speed transmission of nerve impulses in the CNS. MS is the most common autoimmune neurodegenerative disease in subjects between 20 and 50 years of age,<sup>9</sup> and the patient may have one or more of the following types of cells involved of the injury:

- *Pattern 1:* T cells and macrophages are around the capillaries in the lesion, but the oligodendrocytes remain mostly intact and there are no antibodies. It occurs in 15% of patients.<sup>10</sup>
- *Pattern 2:* The lesion presents T cells and macrophages around the capillaries with intact oligodendrocytes but complement activation. It occurs in 58% of patients.<sup>10</sup>
- *Pattern 3:* There are diffuse lesions with inflammation and damaged oligodendrocytes, along with microglial activation and loss of MAG (myelin-associated glycoprotein). There is also partial oligodendrocyte remyelination and apoptosis. It occurs in 26% of patients.<sup>10</sup>
- *Pattern 4:* Lesions show abrupt edges, degenerated oligodendrocytes, and myelin ring. There is no complement activation or MAG loss. It only occurs in 1% of the patients.<sup>10</sup>

MS is classified into several subtypes based on how it develops clinically.<sup>11</sup>



- *Relapsing-remitting (RRMS)*: It is characterized by acute pictures of signs and symptoms that last weeks or months, alternated with periods of complete or partial resolution or the appearance of new signs and symptoms with recoveries. About 85% of people are diagnosed at this point. People aged 20–40 are diagnosed.<sup>11</sup>
- *Secondary-progressive (SPMS)*: Appears 10–20 years after the installation of the relapsing-remitting form. Remissions become infrequent and are usually replaced by a gradual worsening of neurological symptoms over months to years. If neurological sequelae presents, the progression of early lesions is considered. Between 30 and 50% of patients with RRMS eventually develop SPMS.<sup>11</sup>
- *Primary-progressive (PPMS)*: It is a disabling form of the disease marked by a constant worsening of symptoms, usually without definite recurrences or remission periods. About 15% of people with MS have this condition, which is diagnosed in between ages 40 and 60.<sup>11</sup>
- *Progressive-relapsing (PRMS)*: It is a subtype of the primary-progressive form that can have rare relapses superimposed on a slow progression. It is the most aggressive subtype of the disease and affects between 3 and 5% of the cases. Unlike the relapsing-remitting form, PRMS shows a scarcity of brain and spinal lesions on MRI that differs from the patient's pathological, immunological, and clinical manifestations. It returns continuously from the beginning of the disease, presenting periodic severe exacerbations.<sup>11</sup>

## Pathophysiology

In MS, tissue damage and neurological symptoms are the result of an immune mechanism directed against myelin sheath antigens made up of oligodendrocytes lining axons (neuronal extensions). The tissues of the nervous system and the spinal cord are protected by the blood-brain barrier (BBB), which is dysfunctional in these patients and allows macrophages and lymphocytes (T and B) to enter and carry out their autoimmune attack. There is inflammation, demyelination, reactive gliosis, and axonal damage. The most widely accepted hypothesis regarding its origin postulates that MS is the result of a genetic predisposition, an unknown environmental factor and a local or systemic factor that activates the autoimmune T cells. It is believed that this local factor could be certain infections (mostly by Epstein-Barr virus) or low vitamin D levels and little sun exposure. This would cause an autoimmune reaction, triggering inflammation and demyelination reaction. Activated CD4+ appear to adhere to the surface of endothelial cells in CNS vessels and migrate to the CNS, crossing the BBB. This leads to increased expression of cell adhesion molecules, matrix metalloproteinases, and

pro-inflammatory cytokines. Together, they attract additional immune cells, break down the extracellular matrix to aid their migration, and activate autoimmune responses against antigens, such as basic protein, myelin, myelin-associated glycoprotein, myelin oligodendrocyte glycoprotein, proteolipid protein,  $\alpha$ B-crystallin, phosphodiesterases, and S-100 protein. The binding of these target antigens by antigen-presenting cells triggers an immune response that can involve cytokines, macrophages, and complement. Antibodies against antigens found in white matter and oligodendrocytes can cause direct demyelination by cellular immunity by complement activation inducing cytolysis (fragments of antibodies against the basic protein of myelin have been found in patients affected by EM). Or indirectly demyelination by humoral immunity inducing the activation of macrophages and microglial cells that, through the trimolecular complex (formed by T cell receptors, antigens and receptors of the Histocompatibility class II molecule) would produce cytokines, such as factor  $\alpha$  of tumor necrosis and interferon  $\gamma$  that would generate nitro-oxygenation reactions producing amino acids, complement components, or proteolytic and lipolytic enzymes. The immune attack on the myelin strips the axons and thus reduces nerve conduction as it triggers neurological symptoms. Each patient will develop different symptoms depending on the neurons affected, but the disease can be very disabling.<sup>10,12,13</sup>

## Conventional Treatment

The density and opening of internodal Na<sup>+</sup> channels leads to inflammation and edema that release cytokines, adhesion products, and others, as nitrous oxide (NO). These cause demyelination and slow the conduction of nerve impulse through the axons, which eventually triggers the symptoms of the disease. The short-term treatment is based on recover brain functions with the resolution of edema, changes in pH and the reduction of inflammation, while in the long term will be done by the recovery of Na<sup>+</sup> channels, although this recovery will always result in sequelae of the pathology.<sup>10</sup>

*Treatment of the acute phase.* Treatment should not be delayed more than 48–72 hours, and high doses of corticosteroids should be started. Treatment is based on the administration of 6-methylprednisolone 1 g IV for about 5 days, followed by a descending oral regimen of prednisolone 1 mg/kg/day that can range between 15 and 30 days.<sup>10</sup>

*Treatment to prevent the progression of the disease.* There is a wide variety of drugs that cause a nonspecific suppression of the immune system.<sup>10,14</sup>

- Immunosuppressants as azathioprine, cyclophosphamide, cyclosporine, FK506, methotrexate, mitoxantrone, deoxyspergualin, monoclonal antibodies, sulfasalazine, and total lymphoid irradiation.<sup>10</sup>



- Immunomodulators as linomide, immunoglobulins IV, or plasmapheresis in cases of resistance.<sup>10</sup>
- Administration of autologous T-cell clones by irradiation, inducing activated T cell withdrawal.<sup>10</sup>
- Modification of the cytokine system: Among the current treatments for the disease, there is the subcutaneous or intramuscular injection of Interferon B; which has diverse immunomodulatory effects and therefore multiple adverse effects, including influenza, depression, leukopenia, and hepatotoxicity. Two types of interferons are available on the spanish market; 1b which is administered subcutaneously and 1a, the latter for intramuscular administration, with a new variant with a higher dose recently introduced 1a subcutaneously.<sup>10,14</sup> Another subcutaneous injection that is usually given is glatiramer acetate (GA), which has effects on T cells and much fewer adverse effects than interferon B. However, it has not yet reached Mexico.<sup>10</sup>
- Inactivation of inflammatory mediators through inhibition of metalloproteases: In oral treatment there is dimethyl fumarate, which prevents the activation of the nuclear factor 2 transcription pathway and thereby reduces the inflammation of the disease. Another oral treatment is reriflunomide; a pyrimidine blocker that at the molecular level reduces the division of inflammatory cells.<sup>10,14</sup>
- Inhibition of migration through the blood-brain barrier: by blocking adhesion molecules by ICAM-1, VCAM-1, VLA-4 antibodies or by blocking cytokines: natalizumab, a monoclonal antibody that is applied intravenously, attacks  $\alpha$ 4-integrin and thus reduces the entry of lymphocytes to the Central Nervous System to maintain myelin integrity.<sup>10</sup>
- By promoting remyelination: fingolimod; sphingosine receptor modulator that is taken by mouth. Sphingosine is a complex aminoalcohol of great importance, since it is a precursor component of sphingolipids in general. The phospholipid or sphingolipid complex of interest to rescue with the receptor, is sphingomyelin; because it would keep the axons protected.<sup>10,14</sup>

It should be noted that all these oral medications must be given daily and thus are usually annoying for the patient. That is why a drug administered monthly is also mentioned.<sup>14</sup>

## METHODS

*Inclusion and exclusion criteria.* This review contains randomized clinical trials, meta-analyses, and full-text systematic reviews

conducted in humans and rats, published in English and Spanish in the last five years. It excludes non-randomized trials, quasi-randomized trials, case reports, trials written in languages other than English or Spanish, and trials conducted in species other than humans or rats. Articles that do not have concise and well-supported conclusions or that do not talk about the treatment of MS or ALS are also excluded. For clinical trials to be included, they must provide an in-depth breakdown of randomization methods, diagnostic criteria, details of interventions, and efficacy evaluation. The duration of treatment and patient follow-up is unlimited.

*Types of intervention:* Any type of intervention is included as long as it is randomized.

*Data sources and search strategy.* The following databases were searched from February 2015 to February 2020 for studies relevant to this review: PubMed, SciELO and Cochrane. Since each database has its own limits, there was a little variation between the limits in each one, but they all have the same year limits and MeSH keywords. The articles without enough limits for species, language, or studies were analyzed by the researchers. They were discarded if they were not randomized clinical trials, meta-analyses, or full-text systematic reviews conducted in humans and rats, published in English and Spanish in the last 5 years. Articles without concise and well-supported conclusions or not dealing with MS or ALS treatment were excluded. Here we present the limits established on each database. PubMed: The research was made with the MeSH keywords clinical advances, treatment and multiple sclerosis and clinical advances, treatment and amyotrophic lateral sclerosis. The limits were full text, meta-analysis, randomized controlled trial, and systematic review from 2015 to 2020 in humans and other animals in English and Spanish. SciELO: The research was made with the MeSH keywords clinical advances, treatment and multiple sclerosis and clinical advances, treatment and amyotrophic lateral sclerosis. The limits were articles from 2015 to 2020 in English and Spanish. Cochrane: The research was made with the MeSH keywords clinical advances, treatment and multiple sclerosis and clinical advances, treatment and amyotrophic lateral sclerosis. The limits were essays originally published between 2015 and 2020.

*Type of participants:* Neither the age nor the nationality of the subjects involved was taken into account.

*Type of result measurement:* The validity of the results of the studies was determined by detecting systematic errors or biases (selection, performance, performance bias, attrition/loss, attrition bias, or detection biases). The trials correctly designed and carried out were included in the review.



## RESULTS

- PubMed: It gave 64 results for Multiple Sclerosis and 9 results for Amyotrophic Lateral Sclerosis.
- Scielo: It gave 1 result for Multiple Sclerosis and 0 results for Amyotrophic Lateral Sclerosis.
- Cochare: It gave 18 results for Multiple Sclerosis and 0 results for Amyotrophic Lateral Sclerosis.

From the 3 databases PubMed, Scielo y Cochare; there were selected just 12 articles for MS, and 3 articles for AML. So many of the discarded articles, weren't concise, well-supported or did not talk about the treatment of Multiple Sclerosis or Amniotrophic Lateral Sclerosis. Here is the most relevant information of these articles.

## NEW CLINICAL THERAPEUTIC STRATEGIES

### Amyotrophic Lateral Sclerosis

To find a treatment for this deadly disease, several therapeutic targets were actively sought, including kinases (phosphorylase enzymes whose function is to transfer phosphate groups from ATP to a substrate in order to activate or deactivate it) that did not phosphorylate the proteins involved in the pathological pathology as expected and nonsteroidal anti-inflammatory drugs (NSAIDs) that did not reduced the inflammation cascade caused by the active antibodies of the disease, the silencing of key genes, and the modulation or replacement of specific cell populations that cause autoimmunity. However, none have shown significant improvement as clinical trials have yet to define the safety and tolerability profiles of pharmacological, gene, and cellular therapies.<sup>4</sup> On the other hand, a randomized clinical trial investigated the efficacy of oral curcumin supplementation (600 mg/day). It is a natural antioxidant compound that due to its inhibitory power of the activity of histone acetyltransferases (HAT) and its beneficial anticancer and anti-inflammatory effects, was planned to inhibit the HAT activity of anti-inflammatory cells in a double-blind study.<sup>6</sup> The study used two groups: group A received placebo for 3 months and then curcumin for the next 3 months, and group B took the experimental substance for the entire 6 months. The study performed clinical evaluations and measured oxidative stress biomarkers, including oxidative protein products (AOPP), iron reducing capacity (FRAP), and lactate. Group B showed a reduction in AOPPs ( $p < 0.01$ ) not detected in group A. Additionally, the FRAP assay values remained stable in group B, while group A showed a reduction without treatment and a later increase with therapy. In an assay, lactate was lower in group B vs group A ( $p < 0.01$ ). It was concluded that curcumin treatment shows encouraging results that indicate a slight slowdown in the progression of

the disease. It improves aerobic metabolism and oxidative damage, which also contributes to a deeper understanding of the pathogenic mechanisms of ALS.<sup>6</sup>

The nutritional status is an important prognostic factor in ALS. Then, a randomized study analyzed the safety, tolerability, and efficacy of nutritional counseling with or without an application of mHealth to maintain or increase body weight in ALS. In this randomized, open-label, standard-of-care, single-center controlled clinical trial, 78 participants were enrolled. Adults with ALS were randomized to one of three nutritional interventions: advice from their doctor or nurse (standard care), advice from a registered dietitian (RD, in person), or advice supported by the mHealth app. Although nutritional advice from a dietitian has been shown to be safe, it does not help maintain weight significantly better than standard care in patients with ALS.<sup>8</sup> No effective treatment is currently available for acute phase of ALS beyond supportive care with some moderately life-prolonging supportive medications. All the new and significant clinical advances on the treatment to prevent the progression of ALS are shown in Table 1.

### Multiple Sclerosis

Among the most recent works on MS, there is a mouse model that suggests the transplantation of neuron cell precursors can be a good therapy. These immature cells can become neuronal cells and replace the lost myelin sheath. They also have a protective effect against leukemia since they secrete the cytokine leukemia inhibitory factor.<sup>13</sup> There are also several studies that show the effectiveness of drugs such as ocrelizumab, daclizumab, laquinimod, and masitinib. Ocrelizumab is a humanized anti-CD20 monoclonal antibody in phase 3 trials for progressive forms of MS; it selectively targets CD20-positive B cells, key contributors to myelin and axonal damage. In two global multicenter, double-blind, randomized phase-3 trials in 1656 patients with RRMS, OPERA I, and OPERA II, ocrelizumab significantly reduced the number of lesions detected by MRI compared to IFN  $\beta$ -1a. Daclizumab, on the other hand, is a human monoclonal immunoglobulin G1 antibody directed against the CD25 receptor, expressed on active T cells that could prevent the formation of interleukin-2 receptors in MS. It has even been associated with the activation of regulatory CD56 natural killer cells, which potentially destroy activated autologous T cells. This would likely give daclizumab the ability to reduce T cell proliferation. Laquinimod, another possible treatment, is an oral quinolone-3-carboxamide derived from linomide. Although its action mechanism is unclear, it is presumed to reduce leukocyte migration to the CNS, which would prevent neurological deterioration. Last, masitinib is a selective tyrosine kinase inhibitor that controls mast cell survival, migration, and degranulation by inhibiting certain growth and activation signaling pathways.<sup>15</sup>



TABLE 1. Conventional treatment vs clinical advances in amyotrophic lateral sclerosis.

Amyotrophic Lateral Sclerosis Treatment to prevent the progression of the disease	
<ul style="list-style-type: none"><li>• <b>Riluzole:</b> The recommended dose is 50 mg twice a day, taken one hour before or two hours after a meal.<sup>3,7</sup></li><li>• <b>Edaravone:</b> It is given intravenously, with the first round daily for 14 days, followed by a 14-day break, then in subsequent cycles, 10 out of 14 days followed by a 14-day break.<sup>3</sup></li></ul>	<ul style="list-style-type: none"><li>• <b>Diet:</b> oral curcumin supplementation (600 mg/day). In a double-blind study it was concluded that curcumin treatment shows encouraging results that indicate a slight slowdown in the progression of the disease, improving aerobic metabolism and oxidative damage.<sup>6</sup></li><li>• <b>Nutritional counseling:</b> In a randomized, open-label, standard-of-care, single-center controlled clinical trial; adults with ALS were randomized to one of three nutritional interventions: advice from their doctor or nurse (“standard care”), advice from a registered dietitian (RD) (“in person”), or advice supported by a mHealth app. Although nutritional advice from a dietitian has been shown to be safe, it does not maintain weight significantly better than standard care in patients with ALS.<sup>8</sup></li></ul>

Several trials seeking to provide treatments related to non-genetic factors as diet. Such is the case of a meta-analysis of twelve studies and 950 patients that found vitamin D supplementation plays a therapeutic role in the treatment of MS. Although more trials are required to confirm the appropriate dose, it paints a promising picture.<sup>16</sup> Another systematic review from 2017 suggests amantadine provides a small improvement in fatigue for some people with MS. Still, beneficial effects in advanced stages of the disease have not yet been proven.<sup>17</sup> An additional review found that depression and anxiety are the most common comorbidities in MS, each of which affect more than 20% of the population. The prevalence of psychiatric comorbidities is high even at the time of MS diagnosis and increases throughout the course of the disease. This review revealed that symptomatic therapies used to manage MS can cause many mental diseases to patients, like depression and anxiety. They proved that corticosteroids cause transient depression, mania, and psychosis. And the mental effects of interferon are right now under investigation since the concerns about its probability to cause depression.<sup>18</sup>

It has been found that motor and cognitive rehabilitation can improve functional and structural brain plasticity in MS patients. Since by continuously evaluating the brain of patients in rehabilitation programs based on computer-assisted exercises/video games performed in an outpatient setting or at home, and continuously evaluation of brain structure by imaging techniques such as MRIs; changes in white matter microarchitecture, task-related activation and/or functional connectivity were presented after selective and task-oriented training. A relevant correlation was found between improved motor function and brain changes shown in MRI, supporting the hypothesis that training-induced brain plasticity can lead recovery on patients with MS.<sup>19</sup> There wasn't any advances on the acute effective treatment. Since then, the already known treatment will be the one used; 1 gram of 6-methylprednisolone I.V. for 5 days followed by 15–30 days of prednisolone, at a

rate of 1 mg/kg/day.<sup>10</sup> All significant advances on new clinical therapies about treatment to prevent the progression of MS are shown in Table 2.

### Advancements in licensed therapies

Dimethyl fumarate (DMF) was licensed in 2013 as a first-line oral therapy for patients with RRMS. It is highly effective, neuroprotective, and immunomodulatory and shows a favorable benefit-risk profile. However, the effects of DMF on the immune system of MS patients were unclear prior to marketing. Therefore, a systematic review in 2018 clarified the pharmacokinetics of DMF and its effect on the molecular pathways related to immunity. The evidence from the collected studies pointed to a multifactorial working mechanism of DMF treatment in MS that leads to a restored immune balance favoring a more tolerogenic or anti-inflammatory immune profile. DMF reduces the relapse rate, the number of brain injuries, and protects MS patients from further deterioration of motor and cognitive function; in addition, it has an immunomodulatory effect that modifies the altered immune balance of MS. Treatment with DMF selectively reduces CD8+ T cells and inflammatory memory subtypes of T and B cells in MS patients. This is in part due to the restored cytolytic function of CD56<sup>bright</sup> NK cells in DMF-treated MS patients. Furthermore, the expression or production of pro-inflammatory cytokines by T cells and B cells is reduced by shifting the Th1/Th17 response and pro-inflammatory B cells to an anti-inflammatory response. Therefore, treatment with DMF inhibits the activation and proliferation of T cells as well as the expression of antigen presentation and costimulatory markers in B cells.<sup>20</sup>

Cognitive impairment affects 40–65% of patients with MS. Therefore, another study evaluated the effects of fingolimod and IFN  $\beta$ -1b on the progression of cognitive impairment using MRI and clinical outcomes in patients with RRMS for 18 months.

**TABLE 2. Conventional treatment vs clinical advances in multiple sclerosis.**

<b>Multiple Sclerosis</b> <b>Treatment to prevent the progression of the disease</b>	
<ul style="list-style-type: none"> <li>• <b>Immunosuppressants:</b> azathioprine, cyclophosphamide, cyclosporine, FK506, methotrexate, mitoxantoin, deoxyspergualine, monoclonal antibodies, sulfasalazine or even total lymphoid irradiation.</li> <li>• <b>Immunomodulators:</b> linomide, i.v. immunoglobulins or plasmapheresis in cases of resistance.</li> <li>• <b>Administration of autologous T cell clones by irradiation:</b> <ul style="list-style-type: none"> <li>○ Modification of the cytokine system: Among the current treatments for the disease, there is the subcutaneous or intramuscular injection of Interferon B. Two types of interferon are available on the Spain market; 1b which is administered subcutaneously and 1a, the latter for intramuscular administration, with a new variant with a higher dose recently introduced 1a subcutaneously.</li> <li>○ Another subcutaneous injection that is usually given is GA, which has effects on T cells and much fewer adverse effects than interferon B. However, it has not yet reached Mexico.</li> </ul> </li> <li>• <b>Inactivation of inflammatory mediators through inhibition of metalloproteases:</b> <ul style="list-style-type: none"> <li>○ In oral treatment there is dimethyl fumarate and teriflunomide.</li> </ul> </li> <li>• <b>Inhibition of migration through the blood-brain barrier, by blocking adhesion molecules by ICAM-1, VCAM-1, VLA-4 antibodies or by blocking cytokines:</b> <ul style="list-style-type: none"> <li>○ Natalizumab, a monoclonal antibody that is applied intravenously.</li> </ul> </li> <li>• <b>Remyelination promoters:</b> <ul style="list-style-type: none"> <li>○ Fingolimod; sphingosine receptor modulator that is taken by mouth.<sup>10,14</sup></li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>• <b>Neuron cell precursors:</b> these immature cells can become neuronal cells that replace the lost myelin sheath.<sup>13</sup></li> <li>• <b>Monoclonal antibodies:</b> <ul style="list-style-type: none"> <li>○ Ocrelizumab: humanized anti-CD20 monoclonal antibody in phase 3 clinical development of progressive forms of MS that selectively targets CD20-positive B cells, key contributors to myelin and axonal damage. It has significantly reduced the number of lesions detected by MRI compared to IFN beta-1a in phase 3 studies.<sup>15</sup></li> <li>○ Daclizumab: It has even been associated with the activation of regulatory CD56 natural killer cells, which potentially destroy activated autologous T cells: which would give it the ability to reduce T cell proliferation. However, this is not yet confirmed.<sup>15</sup></li> </ul> </li> <li>• <b>Immunomodulators:</b> <ul style="list-style-type: none"> <li>○ Laquinimod: Although its mechanism of action is not clear, it is presumed that it reduces the migration of leukocytes to the CNS, which would prevent neurological deterioration in the patient.<sup>15</sup></li> <li>○ Masitinib: selective tyrosine kinase inhibitor that controls mast cell survival, migration, and degranulation by inhibiting certain growth and activation signaling pathways.<sup>15</sup></li> </ul> </li> <li>• <b>Diet:</b> vitamin D supplementation has a therapeutic role in the treatment of MS. Although more trials are required to confirm the appropriate dose, it paints a promising picture.<sup>16</sup></li> <li>• <b>Symptomatically treatment:</b> <ul style="list-style-type: none"> <li>○ Amantadine may provide a small improvement in fatigue for some people with multiple sclerosis, although beneficial effects in the advanced stages of the disease have not yet been proven.<sup>17</sup></li> <li>○ Motor and cognitive rehabilitation can improve functional and structural brain plasticity in patients with MS. Since by continuously evaluating the brain of patients in rehabilitation programs based on computer-assisted exercises / video games performed in an outpatient setting or at home, by means of imaging techniques such as MRIs; changes in white matter microarchitecture, task-related activation and / or functional connectivity were described after selective and task-oriented training.<sup>19</sup></li> </ul> </li> </ul>





The study included RRMS patients with cognitive impairment randomized (2:1) to fingolimod (0.5 mg daily)/IFN  $\beta$ -1b (250  $\mu$ g every other day). Impairment was assessed using Rao's Brief Repeatable Battery test and the Delis-Kaplan executive function system. MRI parameters, Expanded Disability Status Scale (EDSS) scores, and relapses were measured. Patients (157) were randomized, of which 30 discontinued the study. At month (M) 18, both treatment groups showed improvement in all cognitive parameters. The relapse rate, the total number, and the volume of the lesions enhanced with gadolinium T2/T1 were higher with IFN  $\beta$ -1b, as well as the percentage of change in brain volume during the study. The safety and tolerability of both treatments were similar to previous studies. Both treatments showed improvement in cognitive parameters. Fingolimod demonstrated significantly better effects on MRI parameters and relapse rate. A trial of longer duration and lower dropout rate is necessary to observe the full expression of the differential effects on the cognitive impairment scales that reflect the differences between the groups on MRI. But still, the study confirms the favorable benefit-risk profile of fingolimod.<sup>21</sup>

Another triple-blind, placebo-controlled study evaluated autologous transplantation with adipose-derived mesenchymal stem cells (AdMSCs). The patients were randomized to receive a single infusion of placebo, low-dose (1 x 10<sup>6</sup> cells/kg), or high-dose (4 x 10<sup>6</sup> cells/kg) autologous AdMSC product and were followed for 12 months. Autologous AdMSC infusion is safe and feasible in patients with SPMS. Larger studies and probably an earlier stage treatment would be needed to investigate the potential therapeutic benefit of this technique. However, the study demonstrated that AdMSC infusion is a safe and feasible procedure in patients with SPMS.<sup>22</sup>

An attempt was also made in 2016 to find out whether erythropoietin (EPO), part of an endogenous neuroprotective system in the brain, could be a viable treatment in progressive MS. A phase 2, single-center, randomized, double-blind, placebo-controlled trial was conducted in which 52 patients with SPMS or PPMS were assigned to treatment with recombinant EPO (48,000 IU) or placebo IV 17 times over 24 weeks. No difference was found in the primary outcome between the EPO group and the placebo group since none of the secondary outcomes, neither clinical nor MRI measures showed significant differences.<sup>23</sup> Many studies also proved that active derivatives of vitamin A suppress the formation of pathogenic T cells in patients with MS. Therefore, a 1-year randomized placebo-controlled clinical trial examined 101 patients with RRMS to determine the degree of impact of vitamin A on disease progression in MS. The treated group received 25,000 IU/d of retinyl palmitate for six months followed by 10,000 IU/d of retinyl palmitate for another six months. Results of EDSS and Multiple Sclerosis Functional Composite (MSFC) were recorded at the beginning and end of the study. The results showed that

the mean  $\pm$  SD of the changes in clinically probable multiple sclerosis (CPEM) in the treated group was  $-0.14 \pm 0.20$  and in the placebo group,  $-0.31 \pm 0.19$ . The CPEM improved significantly ( $P < 0.001$ ) in the treatment group. There were no significant differences between the mean  $\pm$  SD of the EDSS changes in the treated ( $0.07 \pm 0.23$ ) and placebo ( $0.08 \pm 0.23$ ) groups ( $P = 0.73$ ). Similarly no significant differences were observed between the mean  $\pm$  SD of the annualized relapse rate in the treated group ( $-0.36 \pm 0.56$ ) and the placebo groups ( $-0.53 \pm 0.55$ ) ( $P = 0.20$ ). Vitamin A then improved the total MSFC score in RRMS patients, but did not change EDSS, relapse rate, or active brain lesions. The study then provides class II evidence that treatment with high-dose EPO is not effective in patients with moderately advanced progressive MS.<sup>24</sup>

GA is an immune modulating medication currently used to treat RRMS and clinically isolated syndrome (CIS). It is a random sized 40–100 amino acid polymer composed of primarily L-alanine, L-lysine, L-glutamic acid, and L-tyrosine. The premise behind its mechanism of action lies in the construct that patients with MS have antibodies directed against myelin basic protein (MBP), a component of the myelin sheaths of neurons within the CNS. Its chemical construct allows GA to mimic MBP and thus be a decoy for the antibodies in these patients, reducing the inflammatory response. The postulates from multiple clinical studies are that GA shifts the immune response from a pro-inflammatory state comprised of Th1 T-Cells to regulatory, non-inflammatory Th2 T-Cells. While GA cannot penetrate the BBB, its ability to induce peripheral Th2 cells and their subsequent crossing of the BBB allows the reduction of further inflammation within the CNS. This action mechanism has been called *bystander suppression*. Thus far, in preclinical levels it has been noted that GA induces a neuroprotective and/or neuro-regenerative effect. The drug increases neurotrophic factors like brain-derived neurotrophic factor (BDNF), which has been discovered to be vital to neuronal and glial cell survival.<sup>25</sup>

It has been shown to have a clear beneficial effect on spasticity in patients with RRMS previously treated with IFN- $\beta$ . In treatment-naïve patients, its effect is less pronounced but without evidence of worsening spasticity. Only two studies have been conducted to evaluate this effect; the first, published in 2010 by Meca-Lallana et al., was a prospective observational pilot study conducted in two cohorts of patients with RRMS and spasticity who were going to be treated with GA: a cohort previously treated with IFN- $\beta$  who switched treatment for reasons of safety or lack of efficacy ( $n = 13$ ) and a cohort of naïve patients ( $n = 15$ ). After 18 months of follow-up and compared to baseline, all patients who switched from IFN- $\beta$  to GA showed a significant reduction in mean scores on the MAS for the right and left hemibodies and in scores of the PSFS and Global Pain Scale. In patients who started GA as the first disease-modifying drug, no change in their degree of spasticity was seen on any of the clinical scales used, probably



because the baseline mean degree of spasticity was very mild and lower than those of patients treated with IFN- $\beta$ . However, they did show a significant reduction in H reflex latency in the left hemibody and H/M ratio in the right hemibody (these are two objective electrophysiological indicators of improvement in spasticity, whose sensitivity, validity and reproducibility have been previously confirmed).<sup>26</sup>

## DISCUSSION

Some vital data for the management of autoimmune neurodegenerative pathologies presented here is important. It must be noted that, once a diagnosis has been made, the patients and their relatives must be informed about the nature of the disease with total clarity and, above all, the recent diagnosis does not imply an unfavorable prognosis in all cases. Secondly, the precautions that people must have, as avoiding exposure to viral diseases, is relevant. The treatment must be multidisciplinary since several areas are involved in diseases. Thirdly, the ideal treatment is to be chosen taking into account the new scientific discoveries regarding the disease in question.

In ALS, no effective treatment was found beyond supportive care with some moderately life-prolonging supportive medications such as riluzole (which inhibits glutamate release, blocking postsynaptic glutamate NMDA and kainate receptors, and inactivating voltage-gated Na<sup>+</sup> channels) and edaravone (small molecule that reduces oxidative stress). Meanwhile, in recent lines of research regarding pathology, a randomized clinical trial investigated the efficacy of oral curcumin supplementation (600 mg / day) and concluded that treatment with this substance shown a slight slowdown in disease progression. But it is need to know the molecular mechanism of the substance in new investigations in order to know how it improves the aerobic metabolism and reduce oxidative damage of the disease. Knowing this we may have more therapeutic ideas that enhance the effects of the curcumin. Other studies did not reveal new therapeutic targets; since the randomized study that looked at the safety, tolerability, and efficacy of nutritional counseling for maintaining or increasing body weight in ALS, showed that nutritional counseling didn't make a change on the weight of the ALS patients who take the counseling nutritional course compared with the standard care ALS patients.<sup>8</sup> Last, the study that analyzed the treatment with kinases, NSAIDs, key gene silencing, and modulation or substitution of specific cell populations promoting autoimmunity did not demonstrate any important therapeutic benefits.<sup>4</sup> Then, the ALS patient still has not found a treatment to cure their disease. It is needed to keep searching new therapeutic dianas in order to prolong lifes of ALS patients more than the few months gained with riluzole and edaravon. In addition, due to the discoveries demonstrated in curcumin; the effect of curcumin needs to be enhanced and empowered with new medicines.

The conventional treatment for MS in the acute phase should not be delayed more than 48–72 hours and must start with high-dose corticosteroids, 6-methylprednisolone 1 g IV, and prednisolone for 5 days. It prevents disease progression and nonspecifically suppresses the immune system. The actual treatments between the ones a doctor who treats a MS patients can choose are immunosuppressants, immunomodulators, the administration of autologous T cell clones by irradiation, the modification of the cytokine system with Interferon B or GA, the inactivation of inflammation mediators by means of the inhibition of metalloproteases with dimethyl fumarate, the inhibition of migration through the blood-brain barrier and the promotion of remyelination with fingolimod. While new clinical therapeutic strategies suggest a transplantation of neuron cell precursors (that replace the lost myelin covering) and drugs that improve the panorama of the disease with monoclonal antibodies, such as ocrelizumab, daclizumab in order to prolong patients life's; other laboratories need to keep searching ways to cure the disease with new therapeutic dianas. Other trials use treatments related to non-genetic factors. A study using vitamin D is still in process because the appropriate dose is yet to be found. Symptomatic therapies used to control MS can cause depression or anxiety. Several reviews have found that corticosteroids can cause transient depression, mania, or psychosis. Pivotal trials of IFN- $\beta$  for MS raised concerns about this therapy, which evidences the need for new therapies that do not cause this type of comorbidities. Similarly, it was concluded that motor and cognitive rehabilitation can improve plasticity in MS patients, as a relevant correlation was found between improved function and brain changes detected by MRI. This supports the hypothesis that training-induced brain plasticity is specifically related to the trained domain.<sup>19</sup>

All this, in conjunction with the advances in therapies already authorized; such as the recent understanding of the pharmacokinetics of dimethyl fumarate or the recent discovery of the positive effects of fingolimod and interferon beta-1b (IFN  $\beta$ -1b) in the progression of cognitive impairment by magnetic resonance imaging; show that MS, although it still has no cure, does have multiple ways of allowing the patient to have an improvement in their prognosis and quality of life compared to previous therapeutic lines.

Scientific advances are so accelerated that even a triple-blind, placebo-controlled study evaluated autologous transplantation with AdMSCs. Autologous AdMSC infusion is safe and feasible in SPMS patients, but larger and probably earlier studies are still necessary to investigate the potential therapeutic benefit of this technique. Other treatments have also been tried and discarded; EPO and vitamin A (in a randomized controlled clinical trial) provided class II evidence that high doses of EPO are not effective in patients with moderately advanced progressive MS.<sup>24</sup>



## CONCLUSIONS

It is necessary to continue searching for more information on the pathophysiology of amyotrophic lateral sclerosis and multiple sclerosis in order to find their main causes and thus the way to reverse them. To date, there are only medications that prolong the patient's life, as riluzole and edaravone for amyotrophic lateral sclerosis and fingolimod, dimethyl fumarate and IFN  $\beta$ -1b for multiple sclerosis. Importantly, a 600-mg dose of curcumin added to the diet in amyotrophic lateral sclerosis has shown to inhibit the activity of histone acetyltransferases in anti-inflammatory cells and help the prognosis. In addition, more studies should be carried out on autologous transplantation with adipose-derived mesenchymal stem cells to investigate their potential therapeutic benefit in phases prior to secondary-progressive multiple sclerosis.

## CONFLICT OF INTEREST

There was no affiliation with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), and non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed and showed in this manuscript.

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