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Multiple sclerosis and experimental autoimmune encephalomyelitis: A review

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ABSTRACT
Multiple sclerosis is a chronic inflammatory autoimmune disease of the central nervous system, characterized by mononuclear cell infiltration, axon demyelination and gliosis in the myelin sheath, with formation of multiple plaques. It affects individuals aged between 25 and 50 years old, female and residents of higher latitudes. The etiology of multiple sclerosis is multifactorial and not fully understood; however, the influence of genetic predisposition and environmental factors on immune dysregulation is recognized. The pathophysiology of the disease is mediated by self-reactive T lymphocytes that respond to autoantigens from the central nervous system. The emergence of multifocal regions of demyelination, axonal loss, loss of oligodendrocytes and astroglial scarring result in impaired neurological function, leading to neurodegeneration. Although there is still no cure for multiple sclerosis, scientific research has provided great advances in therapeutic strategies. Currently there are approaches to attenuate specific signs and symptoms, drugs to control disease relapses and treatments designed to modify or delay the course of multiple sclerosis. Although these drugs show promising effects, they are ineffective in curing the patient. In addition, they present a fundamental problem, which is the non-selective action on the cells of the immune system, which triggers serious side effects. Considering the limitations of studies in humans due to the difficulty of accessing the affected tissues, the use of experimental models that simulate the singularities of multiple sclerosis is a key element for the study of the pathogenesis of inflammation and therapeutic alternatives. Experimental autoimmune encephalomyelitis, an animal model that presents several similarities with pathophysiological, histological and clinical aspects of multiple sclerosis, is the most used model for these studies. Therefore, in this chapter, the aim was to review the historical context, definition, etiology, pathophysiology, clinical manifestations, diagnosis and treatment of multiple sclerosis and, at the same time, address aspects of the timeline, induction, the evolutionary course and the immunopathogenesis of the most studied model for the investigation of the nuances of multiple sclerosis, correlating the similarities and differences between both.

Keywords: Multiple sclerosis, experimental autoimmune encephalomyelitis, neural degeneration, revision.

1 INTRODUCTION

Multiple sclerosis was first reported in the year 1200 in an Icelandic woman and in St. Lidwina of Schiedam (1380-1433). Other accounts reveal the daily struggle British writer W. N. P. Barbellion (1889-1919) with the clinical manifestations of the disease (LANDTBLOM *et al*., 2010). Some writers such as Charles Dickens used fictional characters to document neuroinflammatory disorders in their novels (BRAIN, 1955; PETZOLD, 2013). In 1866, a series of coherent articles on *La sclerose en plates was published* by Jean Martin Charcot, considered the father of neurology at the La Salpétriére hospital in Paris. Charcot elaborated presuppositions about the pathophysiology of the disease, correlating it with the clinic, thus contributing to the creation of the first diagnostic criterion of multiple sclerosis, named Charcot's triad, consisting of nystagmus (involuntary, rhythmic and repetitive ocular oscillations of one or both eyes), ataxia (lack of coordination of movements of different parts of the body) and dysarthria (difficulty in articulating speech). Pierre Marie, Charcot's successor, suggested in 1884 the infectious etiology of multiple sclerosis, which to this day is the most acceptable (MILO; MILLER, 2014).

Multiple sclerosis is a chronic inflammatory autoimmune disease of the central nervous system, characterized by infiltration of mononuclear cells, demyelination of the axon and gliosis in the myelin sheath, with formation of multiple plaques (MILO; MILLER, 2014). Such destruction of the myelin sheath of the axons produces a blockage of the electrical impulse to the target cells, resulting in a wide spectrum of clinical manifestations, ranging from speech disorders to total paralysis (GOVERMAN, 2009). The pathophysiology of the disease is mediated by self-reactive T lymphocytes that respond to central nervous system autoantigens. The emergence of multifocal regions of demyelination, axonal loss, loss of oligodendrocytes and astroglial scars result in deficit of neurological function, leading to a neurodegenerative process (FONTES *et al*., 2014; DIAS *et al*., 2014, DENDROU; FUGGER; FRIESE, 2015; KIPP *et al.,* 2017; FONTES *et al*., 2017; MCGINLEY *et al*., 2018). The disease is characterized by periods of relapse and remission in some people, while a progressive pattern is noticed in others, impairing the quality of life of those affected, because the crises gradually compromise the neurological capacity of the sick (MILO; MILLER, 2014). In the scientific literature it is recognized that multiple sclerosis usually affects a profile of individuals aged between 25 to 50 years of age (although it can occur at all ages), female sex and residents of areas far from the equator (PEREIRA *et al*., 2015).

Recent data from the 2020 Atlas of Multiple Sclerosis, prepared by the International Federation of Multiple Sclerosis with the World Health Organization (WHO), showed that the prevalence of the disease is increasing worldwide, reaching 2.8 million in 2020, with a global prevalence of 35.9 per 100,000 people. This aspect points to the challenges faced by the sick, such as access to diagnosis and treatment. The prevalence of multiple sclerosis is related to geographic distribution, according to a

meta-analysis by Simpson et al. (2019), confirming that increased prevalence of the disease is still strongly associated with increased latitude. As for the prevalence of multiple sclerosis by region of the world, between 2013 and 2020 an increase of 87% was observed in the Americas, 59% in Africa, 58% in Southeast Asia, 38% in the Eastern Mediterranean, 32% in the Western Pacific and 32% in Europe. Europe continues to be the region with the highest incidence (per 100,000 people/year), reaching the value of 6.8, while the Americas register 4.8 and Southeast Asia and Africa have incidence rates of 0.4 (ASCHERIO; MUNGER, 2016; BLOZIK *et al*., 2017; COETZEE; Thompson, 2020; WALTON *et al*., 2020). Brazil, in turn, has an average prevalence of 8.69/100,000 inhabitants and, as in the world, the prevalence varies according to the region of residence of the patient, being lower in the Northeast (1.36 per 100 thousand inhabitants) and higher in the South (27.2 per 100 thousand inhabitants), confirming the relationship between multiple sclerosis and latitude (PEREIRA *et al*., 2015).

The disease usually occurs in young individuals and is more common in females. Global reports indicate that multiple sclerosis is more frequent in women, and in some countries the ratio is four women to one man (COETZEE; Thompson, 2020; WALTON *et al*., 2020). In a systematic review of 28 epidemiological studies from 1955 to 2000, an increase in the incidence of multiple sclerosis in the female/male ratio was found to be increased from 1.4 to 2.3 (ALONSO; HERNÁN, 2008) and, subsequently, a systematic review with meta-analysis also suggested the increased incidence of the disease in women (KOCH-HENRIKSEN; Sørensen, 2010). This difference in the incidence of the disease between genders still has an unknown cause. It is suggested that hormonal factors may be related to this female predisposition to the disease (ABREU *et al*., 2012).

The etiology of multiple sclerosis is multifactorial and not fully clarified (ZAGON; MCLAUGHLIN, 2017), however, the influence of genetic predisposition and environmental factors on the immune dysregulation verified in the pathogenesis of the disease is recognized (ABREU *et al*., 2012; WAUBANT *et al.,* 2019). Therefore, it is impossible to estimate the risk of developing the disease based on genetic susceptibility alone (MUNGER *et al*., 2006).

The genetic component of multiple sclerosis results from the action of common allelic variants in many genes and the emerging contribution of rare variants, thus involving a complex network of molecular and functional interactions. Recently, considerable progress has been made in understanding the genetic basis of susceptibility to multiple sclerosis. Thus, to date, using genome-wide association screens (GWAS), which incorporate large matrices of single nucleotide polymorphisms (SNPs) spread throughout the genome, more than 200 common risk variants located in diverse genomic regions have been identified. (DENDROU; FUGGER; FRIESE, 2015; ANDLAUER *et al*., 2016; DARGAHI *et al* 2017; NOURBAKHSH; MOWRY, 2019). Some *loci* may be related to early pathogenic events, while others may influence the development and progression of the disease. The class II major histocompatibility complex (MHC) was the first *locus* of susceptibility to multiple sclerosis to be

identified and has several independent susceptibility variants (MOUTSIANAS *et al.,* 2015), with the genetic factor with the strongest link with multiple sclerosis being the *HLA-DRB1*15:01 haplotype* (CANTO; OKSENBERG, 2018; WAUBANT *et al.,* 2019). In twin studies, the genetic influence is clearly observed, with the concordance rate for multiple sclerosis in monozygotic twins being 30%, in contrast to 5% for dizygotic twins. With regard to the degree of kinship, the risk of multiple sclerosis in first-degree relatives is about 1 in 40, being 20 times higher than in the general population. For second-degree relatives, the risk is 1 in 100, that is, about 10 times higher than in the general population (WILLER *et al*., 2003).

Regarding environmental risk factors, we can include smoking, obesity, previous contact with the Epstein-Barr virus and vitamin D deficiency, frequently noted in populations of regions with low solar incidence, an aspect that explains the correlation between multiple sclerosis and latitude (ASCHERIO; MUNGER, 2016; CORREALE; FAREZ, 2015; NEW; BATISTA, 2017; FERRE *et al*., 2018; Simpson *et al*, 2019; JAKIMOVSKI *et al*. 2019; WAUBANT *et al*., 2019; Sollid, 2022).

The immunopathogenesis of multiple sclerosis involves the activation of T and B lymphocytes that act against central nervous system antigens, leading to progressive axonal loss, brain atrophy, and neurological and cognitive impairment **(**BIERHANSL *et al.,* 2022). In multiple sclerosis several defects have been identified in the mechanisms of self-tolerance. Failure in the so-called central tolerance mechanisms occurs in the thymus for T cells and in the bone marrow for B cells (DENDROU; FUGGER; FRIESE, 2015). In central tolerance, a dysfunction of the thymic production of antigen-specific T cells was observed, with alterations in the receptors of T cells, favoring autoimmune reactions (WUCHERPFENNIG *et al*., 2009; YIN et al., *2011), in addition to being noted a premature involution of the thymus resulting in the reduced export of virgin regulatory T cells, the fully suppressing regulatory T clone (HAAS* et al., 2007). In peripheral tolerance the failure is linked to co-stimulatory molecules and to transcriptional and epigenetic mechanisms (GONSETTE, 2012).

Consequently, self-reactive cells that escape central tolerance can be activated in peripheral lymphoid organs by autoantigens that present molecular mimicry with some proteins characteristic of the central nervous system, such as myelin proteins (DENDROU; FUGGER; FRIESE, 2015). The basic protein of myelin (MBP), the proteolipid protein (PLP) and the glycoprotein of oligodendrocyte myelin (MOG) are studied as candidates for target autoantigens of lymphocyte reactivity verified in the immunogenesis of multiple sclerosis (HELLINGS *et al*., 2001).

Once activated, virgin CD4+ T cells undergo differentiation into subtype 1 (Th1) and subtype 17 (Th17) helper T cells that secrete inflammation mediators such as interferon-γ (IFN-γ) and interleukin-17 (IL-17), respectively. During the activation process, antigen-presenting cells and T cells produce substances that modulate the immune response. Th1-profile immune responses are commanded by interleukin-12 (IL-12), IFN-γ, and interleukin-18 (IL-18), while Th17-profile immune

responses are mediated by transforming growth factor-β (TGF-β), inteleucine-1β (IL-1β), interleukin-6 (IL-6), and interleukin-23 (IL-23). Activated self-reactive T lymphocytes also have an increased ability to cross the blood-brain barrier due to their high expression of mediators, such as chemokine receptors, adhesion molecules, integrins and cytokines (DENDROU; FUGGER; FRIESE, 2015; MILOVANOVIC *et al*., 2020). Although some cells can cross the blood-brain barrier intact, access to the central nervous system by activated helper T cells occurs only after the blood-brain barrier has been disrupted. The entry of cells is facilitated by some molecules such as intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), E-selectin and metalloproteinase-9 (MMP-9) (PICCIO *et al*., 2002). Central nervous system homeostasis is maintained primarily by controlling cell traffic across the blood-brain barrier. Therefore, the importance of the blood-brain barrier in the early pathogenesis of inflammation of the central nervous system is revealed, an aspect further corroborated by the fact that its endothelial cells induce the differentiation of CD209 dendritic cells and, subsequently, secrete interleukin-12p70 (IL-12p70), TGF-β and IL-6, thus providing the differentiation of virgin cells into effector cells of Th1 or Th17 profile (IFERGAN *et al*., 2008). It is assumed that an autoimmune response that causes overexpression of inflammation mediators in sick individuals, such as interleukin-1 (IL-1), interleukin-2 (IL-2), interleukin-3 (IL-3), IFN-γ, TNF-α and tumor necrosis factor-β (TNF-ß), induces the expression of specific molecules in the membrane of central nervous system cells and activates the phagocytic function of microglia cells, as we will see below (REZENDE; ARRUDA, 1998). It is also worth noting that in addition to CD4+ T cells, CD8+ T cells predominate and proliferate in the central nervous system, exhibiting a relevant role in myelin and oligodendrocyte injury, due to the interaction with MHC class I present in oligodendrocytes, neural bodies and axons (VIEGAS, 2009). In addition, it is known that patients with multiple sclerosis, especially in relapses, have a large number of cytotoxic molecules, such as perforin, expressed by CD8+ T cells (FRISULLO *et al*., 2011).

Th1 and Th17 profile effector cells enter the central nervous system and are reactivated and expanded by the cytokines IL-1β, IL-12, IL-6 and IL-23 produced by the resident microglia and infiltrating monocytes. The degradation of the myelin sheath releases fragments that, in turn, are presented by antigen-presenting cells (APCs) residing in the central nervous system and reactivate CD4+ T cells, resulting in the release of pro-inflammatory cytokines and chemokines. Among the mediators of inflammation secreted, IFN-γ stands out, responsible for the recruitment of CD8+ cells, B lymphocytes and monocytes, leukocytes that also leave the lymph nodes, cross the blood-brain barrier and penetrate the central nervous system. CD8+ cells attack the oligodendrocytes that synthesize myelin, thereby exacerbating neuronal damage. The activation of B lymphocytes by costimulation of T lymphocytes promotes, in turn, the production of autoantibodies related to even more intense damage to the myelin sheath and axon. Microglia ultimately phagocytize the myelin

sheath and release pro-inflammatory cytokines that increase the local immune response. The progression of multiple sclerosis is characterized, therefore, by infiltration of T and B cells, astrogliosis and microgliosis, processes that contribute to structural and functional changes of the nervous system (LASSMANN, 2018; REDFERN, 2021).

In the immune dysregulation of multiple sclerosis, Th17 profile effector cells are attributed a high pathogenic potential in relation to Th1 profile effector cells due to some peculiarities of the Th17 subtype such as: greater proliferative capacity, reduced susceptibility to suppression, greater plasticity of function, expression of a melanoma cell adhesion molecule (MCAM) or CD146 and greater efficiency in migration by the blood-brain barrier (PASSOS *et al*., 2016; BUTCHER; ZHU, 2018) through the secretion of inflammation mediators, such as IL-17, with the ability to damage the integrity of the blood-brain barrier and, consequently, stimulate the migration of cells to the central nervous system (CHENG; CHEN, 2014).

The pathophysiological process of microglial activation in multiple sclerosis is known to induce several phenotypic modifications. Depending on activation, microglia may play a role in the destruction of nerve tissue by the pro-inflammatory M1 phenotype at the onset of multiple sclerosis or tissue repair by the M2 phenotype in later remission of the disease. In response to IFN-γ released by Th1 profile effector cells, the M1 phenotype increases the expression of class II MHC, becomes an antigen-presenting cell, and releases pro-inflammatory cytokines such as IL-1β, IL-6, IL-23, and tumor necrosis factor-α (TNF-α) (KYRAN *et al*, 2018). The M1 phenotype is found primarily in the aggressive and progressive forms of multiple sclerosis and has been histopathologically associated with axonal damage and cortical atrophy in these patients (LASSMANN, 2017; ZETTERBERG, 2017; MASVEKAR *et al*, 2018). The M2 phenotype also presents a phagocytic phenotype and triggers anti-inflammatory responses through the release of interleukin-10 (IL-10) and TGF-β (FILIPPI; ROCCA, 2020; BAR-OR; LI, 2021).

Multiple sclerosis presents variables that reflect pathways to tissue damage (TOBORE, 2021). Inflammation, demyelination and degeneration of axons are changes caused by the main triggering mechanisms of the disease (COMPSTON; COLES, 2008). About 5-10% of the saltatory propagation along the axon is compromised by demyelination. This occurs due to the reduction of internal sodium channels, which constitutes the physiological basis of most of the clinical manifestations of the disease (SCOLDING; FRANKLIN, 1998). For more than a century, neurodegeneration, that is, axonal and/or neuronal damage, has been reported as a component of multiple sclerosis (CHARCOT, 1886), and the identification of neurons, glial cells and myelin patterns in multiple sclerosis and experimental models of the disease is fundamental (VIEGAS, 2009).

In multiple sclerosis, axonal degeneration and destruction of the myelin sheath are responsible for several scattered lesions in the central nervous system, with a predilection for optic nerves, spinal

cord and periventricular white matter (KLEFBECK; NEDJAD, 2003). These lesions spread in time and space, resulting in neurological deficits of variable course (UNPHRED, 2004). The initial lesions in the human brain with the disease are characterized by swelling, vacuolization, fragmentation and separation of myelin from the axon, large influx of microglia and macrophages, which are responsible for the enzymatic degradation of myelin, phagocytosis and apoptosis of oligodendrocytes. Some areas have increased inflammatory activity, active destruction of myelin, remyelination and proliferation of oligodendrocytes from precursor cells; axons, at first, show minimal lesions, but in the long term, they are destroyed (FRANKLIN; FFRENCH-CONSTANT, 2008). The demyelination plaque in any region of the white matter of the central nervous system is the fundamental lesion, presenting variable extension. This plaque has clear characteristics on fresh examination, such as a firm elastic consistency and pink color at the beginning of the disease and, later, grayish, being close to the ventricular surfaces and, in general, limited by the corpus callosum and caudate nucleus, in the dorsolateral region (LOPES *et al*., 1987). Multiple sclerosis has specific components of the lesion that include inflammation of the blood-brain barrier, demyelination after direct destruction of myelin and/or oligodendrocytes, axonal damage, cortical involvement, remyelination, and gliosis. These factors can be observed depending on the phase or clinical stage of the lesion, since classically the active lesions imply in some degree of active damage of the myelin, identified by the presence of its digestion by macrophages (BRUCK *et al*., 1995). The presence of multifocal inflammatory infiltrates (T cells, B cells and macrophages) in the central nervous system is another histopathological marker associated with the degradation of myelin, oligodendrocytes and axons, as well as reactive astrogliosis and microglia activation (FROHMAN; RACKE; RAINE, 2006; MUNGER *et al*., 2006).

Depending on the affected area of the central nervous system, multiple sclerosis may appear as episodic seizures or as a continuous progression (DUFFY; LEES; MOALEM-TAYLOR *et al.,* 2014), affecting mental health and giving rise to musculoskeletal disorders that contribute to the reduction of the quality of life of people affected by the disease (LO *et al*., 2021). The clinical manifestations of multiple sclerosis involve cognitive changes, signs and symptoms of pyramidal syndrome (weakness, spasticity, unilateral or bilateral clonus, hyperreflexia and Babinski's sign), cerebellar dysfunctions with impaired balance and motor coordination, sensory changes such as paresthesia (tingling or numbness) accompanied or not by superficial and deep hypoesthesia in one or more limbs, paroxysmal signs and symptoms (dysarthria, ataxia, dysclonus or tonic spasms and paroxysmal pains such as trigeminal neuralgia), visual disturbances (reduced visual acuity, diplopia and scotomas), psychiatric disorders, sphincter involvement (with urinary and/or fecal incontinence or retention) and sexual dysfunction (OLIVEIRA; SOUZA, 1998).

Multiple sclerosis is associated with varied evolutionary courses. Currently, four forms of presentation of the disease are considered, also known as types or phenotypes, according to the

classification postulated by the *International Advisory Committee on Clinical Trials of Mutiple Sclerosis* in 2013. Clinically isolated syndrome (CIS) results from inflammation and demyelination in the central nervous system and represents the first episode of neurological clinical manifestations lasting at least 24 hours. The relapsing-remitting phenotype (RR) is characterized by episodes of neurological dysfunction followed by partial or complete remission. The secondary-progressive phenotype (SP) follows the initial course of the RR type, but is characterized by a progressive worsening of disability over time. In the primary-progressive phenotype (PP), finally, progressive worsening occurs from the beginning of multiple sclerosis, without relapses. The RR, SP and PP forms may present four variants according to inflammatory activity or disability progression: non-progressive/non-active, non-progressive/active, progressive/non-active, progressive/active. Although not considered a multiple sclerosis phenotype, radiologically isolated syndrome (RIS) has been used to classify individuals with abnormalities on magnetic resonance imaging of the brain and/or spinal cord consistent with multiple sclerosis lesions that are not explained by another diagnosis and that do not present current or past neurological signs and symptoms or abnormalities found on neurological examination (LUBLIN *et al*., 2014). Not infrequently, these individuals undergo magnetic resonance imaging because of random complaints and lesions similar to those observed in multiple sclerosis are found unpretentiously. The study by LEBRUN-FRENAY *et al*. (2020) showed that just over half of people with RIS develop multiple sclerosis within ten years, which reveals the indispensability of health professionals not to neglect suspicious findings.

Currently, there is no specific diagnostic test for multiple sclerosis. Although MRI scans of the brain and spinal cord and cerebrospinal fluid analysis can help, diagnosis is still based on clinical criteria (ARRAMBIDE *et al*., 2019; SOLOMON *et al*., 2019; SALAZAR *et al*., 2022). This occurs because the disease is heterogeneous in terms of clinical manifestations, course and progression of disability. In most cases, after an initial phase characterized by reversible episodes of neurological dysfunction, clinical disability and cognitive impairment become irreversible. The diagnosis of multiple sclerosis requires a careful exclusion of alternative diagnoses and a demonstration of a pathological process of dissemination in space and time (THOMPSON *et al*., 2018).

The diagnosis of multiple sclerosis can be made using McDonald's criteria. The first set of criteria was published in 2001 by a team led by Professor Ian McDonald (MCDONALD *et al*., 2001). They have been extensively reviewed, the most recent version being published in 2017 (THOMPSON *et al*., 2018). The most current reviews did not change the diagnosis of multiple sclerosis, but made it possible for the diagnosis to be made early in the course of the disease. This allows the patient to have access to appropriate treatment early. The main requirement for the diagnosis of multiple sclerosis is evidence of damage to the central nervous system that spreads in time and space. This means showing that the injury occurred on different dates (Dissemination in time or DIT) and in different parts

(Dissemination in space or DIS), thus favoring the distinction of the disease from other neurological conditions. The McDonald criteria use MRI evidence and suggest that this imaging test be performed by all individuals with suspected multiple sclerosis. The lesions can be found even in oligosymptomatic or asymptomatic people, a characteristic that is evidence of DIS. The presence of oligoclonal bands in the cerebrospinal fluid is also a great marker for multiple sclerosis, as it evidences previous activity of the disease and thus can be used as evidence of DIT (THOMPSON *et al*., 2018; HARTUNG *et al*., 2019; ARRAMBIDE *et al*., 2019). In patients with multiple sclerosis, an increase in antibodies, especially immunoglobulin G (IgG), antibodies against oligodendrocyte and myelin glycoproteins, and activated complement components was evidenced in the cerebrospinal fluid (LALIVE *et al*., 2006; LUCCHINETTI *et al*., 2000; LUTTEROTTI; BERGER; REINDL, 2007).

Although there is still no cure for multiple sclerosis, scientific research has provided major advances in therapeutic strategies. Currently there are attenuating approaches to specific signs and symptoms, drugs for the control of disease relapses, and treatments designed to modify or slow the course of multiple sclerosis. Drugs capable of altering the course of multiple sclerosis are called disease-modifying therapies (DMTs) (FILIPPI; ROCCA, 2020). Even with the correct use of medications, not all patients are responsive, considering the heterogeneity of the disease. Despite progress in treatment, the rate of progressive disability and early mortality is still worrisome (GHOLAMZAD *et al*., 2018; HAUSER; CREE, 2020). In addition, adverse effects and high cost are limiting factors. In Brazil, a study conducted with patients with multiple sclerosis, was determined an estimate of total average annual cost of R $ 33,872.00 per patient (KOBELT *et al*., 2019). Other sources show that, in Brazil, the treatment of multiple sclerosis conditions an average annual expenditure of approximately 38 thousand reais per patient. Depending on the severity of the disease and the perspective adopted, however, the costs can vary from 6500 reais to 157 thousand reais (SILVA *et al*., 2016). Spending on disease-modifying therapies for the treatment of multiple sclerosis ranked in 2014 and 2015 the eighth place of highest drug expenditures in the United States of America (USA), according to the report published by the Quintiles IMS Institute in 2015 (AITKEN *et al*., 2016). Thus, it is essential to prospect for effective and clinically and economically viable therapeutic alternatives.

The management of multiple sclerosis can be complex and involve pharmacological and non-pharmacological conducts, requiring a coordinated action by a multidisciplinary health team (BRASIL, 2021). Clinical improvement, increased functional capacity, reduction of comorbidities and attenuation of clinical manifestations are the goals of drug treatment. Glucocorticoids are used in the management of relapses and show short-term clinical benefit by reducing the intensity and duration of acute episodes (GAJOFATTO; BENEDETTI, 2015). In the last two decades, the emergence of drugs active in reducing outbreaks and/or disease progression, the so-called immunomodulators and immunosuppressants, in turn, represented a significant evolution in the treatment of multiple sclerosis

(BRASIL, 2021). In the course of the disease, modifying therapies promote the decrease of circulating immunogenic cells, the suppression of their adhesion to the epithelium and, consequently, the reduction of their migration to the parenchyma and the resulting inflammatory response (TABANSKY *et al*., 2015). Among the drugs used and approved by the National Health Surveillance Agency (ANVISA) for use in Brazil until April 2020, contained in the Clinical Protocol and Therapeutic Guidelines (PCDT) of multiple sclerosis, we find teriflunomide, dimethyl fumarate, fingolimod, natalizumab, interferon beta and glatiramer acetate (BRASIL, 2021).

Teriflunomide is the drug indicated as the first option for the treatment of patients with multiple sclerosis RR phenotype. It is an immunomodulator with anti-inflammatory properties and promoter of selective and reversible inhibition of the mitochondrial enzyme dihydro-orotate dehydrogenase. This enzyme occupies the fourth position of the pyrimidine biosynthetic pathway, consequently causing the inhibition of new synthesis of certain substances and a subsequent cytostatic effect on the proliferation of T lymphocytes (GENZYME A SANOFI COMPANY, 2016; KLOTZ *et al*., 2019). However, in patients with multiple sclerosis, the exact mechanism of action for therapeutic effects is still unknown and evidence suggests that it involves a reduction in the number of activated lymphocytes capable of migrating to the central nervous system (BRASIL, 2017; GENZYME A SANOFI COMPANY, 2016). The choice of teriflunomide for the treatment of patients with multiple sclerosis RR phenotype was based on evidence of the safety and efficacy of teriflunomide compared to current first-line therapeutic options for this clinical presentation of the disease. According to the recommendation report of the National Commission for the Incorporation of Technologies in the Unified Health System (CONITEC), no significant differences were found regarding efficacy and safety between teriflunomide and interferons-beta or glatiramer acetate (SPENCER *et al*., 2015). Treatment with teriflunomide can lead to adverse reactions such as headache, diarrhea, nausea, alopecia, changes in the value of systemic blood pressure, decrease in leukocytes, elevation of liver enzymes, in addition to contributing to the worsening of pre-existing diseases such as interstitial lung disease (BRAZIL, 2017; GENZYME A SANOFI COMPANY, 2016).

Dimethyl fumarate is a first-line drug for the treatment of multiple sclerosis and has a mechanism of action that is not fully understood. Its clinical efficacy has been mainly attributed to a modulating effect on T cells. dimethyl fumarate was found to mitigate the number of circulating T cells, with a disproportionate reduction of the CD8+ subset. Corroborating these direct effects on circulating T cells, studies indicate that dimethyl fumarate contributes to the reduction of the pro-inflammatory activity of antigen-presenting cells, such as monocytes and dendritic cells (KORNBERG *et al*., 2018; SCHULZE-TOPPHOFF *et al*., 2016). The treatment done with Fumarate of methyl can lead to flushing and gastrointestinal events with an incidence ≥ 10%, in addition to other reactions with an incidence between 1% and 10 %, such as leukopenia, lymphopenia, burning sensation, hot

flash, vomiting, gastritis, itching, Proteinuria and increased aminotransferases (BARBUGIANI, 2015; BRAZIL, 2017).

The acetate of Glatiramer is a first-line drug in the treatment of multiple sclerosis RR phenotype and exerts an action immunomodulatory and neuroprotective. It is known that treatment with acetate of Glatiramer induces an increase in the levels of cytokines with activity anti-inflammatory drugs such as interleukin-4 (IL-4), IL-10 and TGF-β, in addition to a reduction in the levels of TNF-α, whose activity is pro-inflammatory (RACKE; LOVETT-RACKE, 2011). Treatment with acetate of Glatiramer may lead to adverse events such as flu, infection, anxiety, depression, vasodilation, dyspnoea, nausea, Rash cutaneous arthralgia, back pain, asthenia and chest pain with an incidence ≥ 10%. Among the effects whose incidence is around 1% and 10%, Found: weight gain, tremors, eye disorders, palpitations, tachycardia, vomiting, skin disorders, chills, edema of the face and vaginal candidiasis (BRAZIL, 2017; TEVA, 2014).

Interferons are cytokines with antiproliferative, immunomodulatory and antiviral functions that are categorized into 3 classes: type 1 (α and β), type 2 (γ) and type 3 (λ) (KNUTH *et al*., 2019). Type 1 interferons can be produced by dendritic cells, such as IFN-α, and also by fibroblasts, such as IFN-β (REDER; FENG, 2014). Beta interferons are included in first-line drugs for the treatment of multiple sclerosis RR phenotype, and are made available by the Brazilian Unified Health System (SUS), including interferon-β-1a (IFN-β-1a) and interferon-β-1b (IFN-β-1b) (BRASIL, 2021). The use of interferons can lead to side effects such as flu-like syndrome (accompanied by fever, chills, myalgia, indisposition), psychic disorders, headache, abdominal pain, urinary incontinence, menstrual changes, rash and even reaction at the injection site (BAYER, 2016; BIOGEN, 2017). The monthly cost of treatment per person ranges from R$3,660.00 to R$4,472.00 (GANDRA, 2019).

Natalizumab is a humanized monoclonal antibody, immunoglobulin G4 (IgG4), which acts by preventing the migration of cells across the blood-brain barrier by binding to integrin alpha 4 beta 1 (VLA-4) present in lymphocytes. This process prevents interaction with the adhesion molecule VCAM-1 expressed by the vascular endothelium (ELICES *et al*., 1990). Therefore, the natalizumab acts as a selective inhibitor of lymphocyte migration across the barrier hematoencephalic (HORGA; TINTORÉ, 2011), being usually prescribed in case of therapeutic failure or associated toxicity (intolerance, hypersensitivity or other side effect) to first- and second-line drugs in patients with multiple sclerosis RR phenotype. In addition, this drug becomes the first treatment option in multiple sclerosis RR phenotype in situations where the disease is in high activity (ENGELHARDT; KAPPOS, 2008). The use of the drug natalizumab may cause adverse reactions such as nausea, urticaria, dizziness, headache, stiffness associated with infusions, arthralgia, fatigue, gastroenteritis, vaginitis, depression, abdominal discomfort, and diarrhea. Such effects have an incidence ≥ 10% in patients who use the drug. Liver damage and hyperbilirubinemia are also described in the scientific literature and

monthly monitoring of the patient's blood count is necessary due to serious reported cases of hemolytic anemia (BIOGEN, 2018).

Fingolimod is a synthetic structural analogue of sphingosine 1-phosphate (SOBIERA, 2010). Highly lipophilic, fingolimod is a prodrug metabolized *in vivo* by the action of the enzyme sphingosine kinase on the active metabolite fingolimod-phosphate, a non-selective modulator of sphingosine 1-phosphate receptors. The reduction in inflammatory activity and myelin-specific autoimmune responses that occur with the use of fingolimod are caused by blocking the migration of T lymphocytes from lymph nodes to the central nervous system (NOVARTIS, 2015; VOLPI *et al*., 2019). Treatment with fingolimod may progress with infections, macular oedema, and transient atrioventricular blocks. Among the adverse reactions with an incidence ≥ 10%, we find headache, increased liver enzymes, diarrhea, cough, flu-like syndromes and back pain (NOVARTIS, 2015). Given the numerous side effects caused by synthetic drugs currently used for multiple sclerosis, the need to investigate new natural alternative medicines (MOJAVERROSTAMI is highlighted) ., 2018).

Although the aforementioned drugs show promising effects in the treatment of multiple sclerosis, they are ineffective in curing the patient. In addition, they present a fundamental problem, which is the non-selective action on the cells of the immune system, which triggers serious side effects such as progressive multifactorial leukoencephalopathy, skin rashes, increased rates of infections and ulcers, in addition to the treatment having long duration and high costs. For patients affected by multiple sclerosis, these variables lead to low adherence to treatment (JONES; COLES, 2010; PLATTEN; STEINMAN, 2006). Thus, the prospection of effective therapeutic alternatives with fewer adverse effects and less costs is necessary.

Considering the limitations of human studies due to the difficulty of access to the affected tissues and the rare performance of autopsies, the use of experimental models that simulate the singularities of multiple sclerosis, in this sense, is a key piece for the study of the pathogenesis of inflammation and autoimmune diseases of the central nervous system (MCGINLEY *et al.,* 2018; MILOVANOVIC *et al*., 2020; BIRMPILI *et al*., 2022). Experimental models of multiple sclerosis can be induced by autoimmunity (such as experimental autoimmune encephalomyelitis, the most studied prototype), viral infections, or exposure to toxins, and although they have advantages and disadvantages, none fully replicate the stages of the disease (BJELOBABA et al., 2018). Specifically, experimental autoimmune encephalomyelitis, an animal model that presents several similarities with pathophysiological, histological and clinical aspects of multiple sclerosis, is induced via active immunization or adoptive transfer of reactive CD4+ T cells against myelin. According to the type of animal used and the material chosen for induction, there are different variations of the experimental autoimmune encephalomyelitis model (ROBINSON *et al*., 2014; KIPP *et al*., 2017; GLATIGNY;

BETTELLI, 2018), in an attempt to reproduce, in animals, the changes observed in multiple sclerosis in humans (SLOANE; LEDEBOER, 2009).

Most often, the study of the pathogenesis and treatment of diseases initially involves in vitro assays*, and after a screening, the best molecules are transferred to the* in vivo scale. Therefore, animals are the beginning for investigations of pharmacological mechanisms of action. Some studies resulting from the process in question have already provided important information related to physiology, immunology, cancer cure, Alzheimer's, acquired immunodeficiency syndrome (AIDS) and others (PEREIRA *et al*., 2020). In 1933, there was the description of the first model of autoimmune response from immunization with myelin of the central nervous system by Thomas Rivers (EPPS, 2005), who used repeated injections of rabbit brain extract in rhesus monkeys. This event boosted the reproduction of histopathological changes and clinical manifestations similar to those identified in multiple sclerosis in experimental models induced by the transfer of sensitized T lymphocytes or through active immunization with whole myelin proteins, myelin epitopes or fusion proteins (BATOULIS *et al*., 2011; BERNARD *et al*., 1997; LININGTON et al., 1992), antigens normally emulsified in adjuvant, such as Freund's Complete Adjuvant (CFA) and Freund's Incomplete Adjuvant (IFA) (BATOULIS et al., 2011). Thus, the experimental autoimmune encephalomyelitis model was consolidated. Inflammation in the central nervous system, demyelination of neurons, and motor changes that are present in multiple sclerosis are observed in this prototype of the disease (AL-OMAISHI; BASHIR; Gendelman, 1999; BAXTER, 2007), an aspect that proves the effectiveness of the referred model for the evaluation of the therapeutic potential of new drugs (SLOANE; Ledeboer, 2009; OLECHOWSKI et al, 2010).

Normally, in the experimental model stimulated by active immunization, the subsequent process involves an induction phase, in which activation of CD4+ T cells specific for the myelin epitope occurs after immunization, and an effector phase, with several stages: (1) migration of myelin-specific T cells to the central nervous system; (2) production of cytokines and chemokines by myelin-specific T cells; (3) activation of peripheral monocytes/macrophages and resident microglial cells of the central nervous system by inflammation mediators secreted by myelin-specific T cells; (4) demyelination of axonal tracts of the central nervous system via phagocytic activity of activated mononuclear cells and cytotoxic effects of inflammation mediators secreted by myelin-specific T cells and monocytes, such as IFN-γ, TNF-α, TNF-β, IL-17 and nitric oxide (NO) (MILLER; KARPUS; Davidson, 2007). In parallel, in the experimental model by adoptive transfer, the effector phase is modulated and there is no induction phase, since there is introduction of previously activated myelin-specific T cells in a healthy animal (MILLER; KARPUS; Davidson, 2007).

The popularity of the experimental autoimmune encephalomyelitis model for the study of multiple sclerosis presents clear reasons: (1) this is the first animal model for this purpose; (2) it is easily induced in many species (as in the syngenic mouse strains C57BL/6, SJL/J and PL/J); (3) the

appearance of clinical manifestations, such as paralysis and loss of tail tone (in rodents), has been reported in several studies; (4) MBP, an important autoantigen used in the induction of the model, is easy to extract and purify, besides being abundant in the nervous tissue and having a small size (the molecular weight is approximately 17 kDa in murine products), allowing the identification of critical determinants (SILVA; OF PAULA; FERREIRA, 2008; YANG, 2003).

The animals used to obtain the experimental model include non-human primates and rodents (mice, rats, and guinea pigs) (BJELOBABA et al., 2018; LINKER; LEE, 2009).

Experimental autoimmune encephalomyelitis by active immunization is induced in rats (commonly of the Lewis or Dark Agouti strains) with MBP or one of its encephalitogenic epitopes, thus resulting in the infiltration of mononuclears into the spinal cord, brainstem, and cerebellum, but not into the brain (ROBINSON *et al*., 2014). Lewis rats are uniformly susceptible to low doses of MBP (5-25 μg) and have a predictable onset time for disease onset, which is acute and spontaneously recovering, but these animals are resistant to attempts to reinduce the model (SWANBORG, 1995; WILLENBORG, 1979). In the case of the resistant strain of Brown-Norway rats, the disease arises from immunization with the extracellular domain of MOG in CFA and, after 10 days, it is noticeable the appearance of a fulminant clinical picture of the disease associated with diffuse demyelination and inflammatory infiltration containing polymorphonuclear cells and eosinophils (STEFFERL *et al*., 1999; Robinson *et al*., 2014).

In mice, the most frequently used animals (ROBINSON *et al*., 2014), experimental autoimmune encephalomyelitis by active immunization can be induced with intact proteins or with peptides of three myelin proteins, MBP, PLP and MOG. In the SJL (H-2s) strain of mice, immunization may involve MBP, PLP, or peptides corresponding to the immunodominant epitopes of MBP (MBP 84-104), PLP (PLP 139-151 and PLP 178-191), and MOG (MOG 92-106). In these animals, there is a prodromal period of 10-15 days followed by a clinical picture of ascending RR phenotype characterized at an initial moment by paralysis in the tail and hind legs, with progression of paralysis to the front legs, concomitant with weight loss. In PL/J (H-2u) and B10.PL (H-2u) mice, on the other hand, the disease is acute and self-limited, with no clinical recurrences. In this lineage, the expression of the disease is with courses of RR phenotype characterized by paralysis. In the C57BL/6 (H-2b) strain of mice, immunization occurs with the peptide corresponding to the immunodominant epitope of MOG (MOG 35-55) and the clinical course is chronic and progressive (MILLER; KARPUS; Davidson, 2007; Robinson *et al*., 2014).

While in experimental models by active immunization the robust immune response caused by the adjuvant itself may be a confounding factor, in experimental models induced by adoptive transfer of specific T cells activated in *vitro* by an encephalitogenic peptide this does not happen, since only blast cells are injected intravenously or intraperitoneally into virgin or immunodeficient mice

(ROBINSON *et al*., 2014). Another advantage of induction by adoptive transfer is the localization of populations of T cells in *vivo in* the course of the disease, since the transferred cells can be labeled with dyes or fluorescent proteins that enable the screening of encephalitogenic T cells (ROBINSON *et al*., 2014). In rats of the Lewis lineage, the onset of the disease occurs 3-4 after the adoptive transfer, reaching a peak in 1-2 days and, subsequently, a complete remission in the sequential days, representing a model of acute disseminated encephalomyelitis, with a purely inflammatory pattern and minimal demyelination of the central nervous system (LINKER; LEE, 2009). In the case of mice, the adoptive transfer of the disease may also include transgenic animals with T cell receptors (TCR) (for example, C57BL/6 2D2 MOG35-55-specific or SJL/J 5B6 PLP139-151-specific), which enables the study of specific T cells of the myelin antigen (ROBINSON *et al*., 2014).

From the above, it is noticeable that the expression of experimental autoimmune encephalomyelitis is different in rats and mice, which are usually preferred by researchers, since the histopathological findings in rats immunized with MBP include perivascular infiltration of mononuclear cells in the spinal cord and brainstem, as well as in the parenchyma of the central nervous system, but demyelination is minimal, while in mice immunized with MBP we found perivascular inflammation by mononuclear cells and demyelination, findings congruent with the pattern of multiple sclerosis (MARTIN; MCFARLAND; MCFARLIN, 1992; SWANBORG, 1995; YANG, 2003). In addition, the susceptible strains of SJL/J and PL/J mice are not resistant to disease re-induction, and it is possible to induce the chronic RR phenotype. However, the variability in the incidences and times of onset of the disease, together with the need to use adjuvants for the induction of the experimental model, are disadvantages of mice in relation to rats (SWANBORG, 1995; YANG, 2003).

Currently, the experimental autoimmune encephalomyelitis model in C57BL/6 mice is one of the most widely used in scientific research in neuroimmunology, with more than 100 publications in recent years (LINKER; LEE, 2009). Induction, in this case, occurs via immunization with a subcutaneous injection of an emulsion composed of MOG 35-55 and CFA, accompanied by intraperitoneal injection of pertussis toxin. The T cells are then activated in the periphery and migrate to the central nervous system through the blood-brain barrier, being reactivated and then commanding subsequent inflammation. The administration of pertussis toxin increases the permeability of the blood-brain barrier and, consequently, facilitates the migration of lymphocytes to the central nervous system, inducing an earlier onset and an intensification of the signs and symptoms of experimental autoimmune encephalomyelitis (HASSELMANN *et al*., 2017; AHARONI *et al*., 2021; HUNTEMANN *et al*., 2022). C57BL/6 mice are quite useful in inducing chronic and severe experimental autoimmune encephalomyelitis, especially when applying MOG as a trigger. The lymphocytes of C57BL/6 mice exposed to this antigen express a higher number of T cell receptors for MOG and a higher titre of anti-MOG antibodies, resulting in a more severe form of the disease

(AHARONI *et al*., 2021; KIPP *et al*., 2017; CONTARINI; GIUSTI; SKAPER, 2017), characterized by inflammatory and demyelinating lesions in the optic nerve, brain, and spinal cord. Inflammatory infiltrates are perivascular and consist mostly of macrophages and T lymphocytes, and some degree of humoral response can be observed with the formation of significant titers of anti-MOG antibodies (KIPP *et al*., 2017; AHARONI *et al*., 2021). MOG is expressed only in the central nervous system and is located in cell bodies and oligodendrocyte processes, in the outer layer of the myelin sheath (KROEPFL *et al*., 2002). Moreover, it is only found in the retina, brain and spinal cord and is only expressed at the end of myelination, and is not found in peripheral nerves (SOSPEDRA; MARTIN, 2005). This protein belongs to the superfamily of immunoglobulins and has 245 amino acids, whose sequence is highly conserved between rodents and humans, with approximately 89% homology between species (DE ROSBO; MENDEL; BEN-NUN, 1995). Because of its strategic location, it is directly accessible to antibodies and is therefore relevant as a target for the cellular and humoral immune responses of multiple sclerosis (SOSPEDRA; MARTIN, 2005). Initially, the induction of experimental autoimmune encephalomyelitis with MOG was obtained in Lewis rats by LINNINGTON et al. (1984), with reports of pathophysiological processes similar to those of multiple sclerosis, including encephalitogenic T cells and demyelination with axonal damage (LININGTON et *al*., 1993; Stork *et al*., 1998). Subsequently, the work of ADELMANN *et al*. (1995) reported that the epitope with 21 amino acids at MOG position 35-55 was recognized by the immune system. The C57BL/6 strain was susceptible to the peptide MOG35-55 and the appearance of clinical manifestations occurred from the 14th day after induction, presenting a chronic evolution and inflammation mediated by T, B cells and macrophages in the central nervous system (BERNARD *et al*., 1997). The leukocyte adhesion to the cerebral microvasculature that occurs on the 14th day after induction correlates with the clinical findings, since this mechanism is involved in cell migration to the central nervous system, with the participation of the chemokines CCL2 and CCL5 (DOS SANTOS *et al*., 2005).

In the scope of clinical manifestations, due to the preferential attack of the spinal cord, animals affected by experimental autoimmune encephalomyelitis course with an ascending pattern of flaccid paralysis involving the tail, hind legs and front paws, with evolution to quadriplegia and death (BATOULIS *et al*. 2011). In the experimental model in question, the genesis of the clinical manifestations is centered on the entry of immune cells into the central nervous system and with the concomitant production and activity of inflammation mediators, factors that contribute to the progression of experimental autoimmune encephalomyelitis. In lesions of the central nervous system, cells such as Th1 and Th17 are able to orchestrate the influx of immune cells via mediator secretion (GLATIGNY; BETTELLI, 2018; VAN KAER *et al*, 2019). Immune system mediators can be pro-inflammatory or anti-inflammatory, and may, respectively, contribute to disease progression or suppression of the self-reactive immune response (JAHAN-ABAD *et al*., 2019).

Dendritic cells, infiltrating macrophages, B lymphocytes and resident microglia of the central nervous system can express the MHC class II molecule and the co-stimulatory molecules CD80 and CD86, thus provoking the initiation and progression of experimental autoimmune encephalomyelitis, in a manner analogous to multiple sclerosis, while CD11c+ cells present themselves as potent APCs, aiding in the proliferative response of T lymphocytes (GOVERMAN, 2009; DONG; YONG, 2019; JURGA; PALECZNA; KUTER, 2020). In experimental autoimmune encephalomyelitis, in particular, it should be noted that dendritic cells and infiltrated macrophages function as more efficient APCs than microglia, resident cells of the central nervous system (WLODARCZYK *et al*., 2014).

As in the pathogenesis of multiple sclerosis, in experimental autoimmune encephalomyelitis we find CD4+ T cells, specifically IFN-γ secreting Th1 cells and IL-17 secreting Th17 cells, in addition to CD8+ T cells (GOVERMAN, 2009; BECHER; SEGAL, 2011). The production of pro-inflammatory cytokines (IFN-γ and IL-17) is induced by CD11+ cells (GARBERS *et al*., 2018). Th1 cells have a pathogenic role in experimental autoimmune encephalomyelitis through the production of IFN-γ in the central nervous system, a crucial cytokine of immuno-stimulation or modulation of Th1 cells (JAHAN-ABAD, 2019). During the activity of multiple sclerosis and experimental autoimmune encephalomyelitis in the lesions, IFN-γ is found at increased levels, a factor associated with an inflammatory response mediated by IFN-γ-producing Th1 cells (LIBLAU; SINGER; MCDEVITT, 1995). IFN-γ regulates the expansion, activation, homeostasis, and survival of T cells (MILLER; MAHER; Young, 2009). Itis also a key player in the induction of experimental autoimmune encephalomyelitis by the activation of macrophages, increased leukocyte adhesion and release of TNF-α and other cytokines (DEGLIANTONI *et al*., 1985; BECHER; SPATH; Goverman, 2017). IFN-γ produced by resident microglia and infiltrating monocytes is also responsible for reactivating Th1 and Th17 cells that enter the central nervous system, recruiting CD8+ cells, B lymphocytes and lymph node monocytes to cross the blood-brain barrier (LASSMANN, 2018).

It is also reported in the scientific literature that the adoptive transfer of IL-12p70-polarized T cells to virgin hosts results in autoimmune encephalomyelitis characterized by ascending paralysis associated with macrophage-rich infiltration and up-regulation of the enzyme nitric oxide synthase 2 (NOS2) (KROENKE *et al*., 2008). IL-12, secreted mostly by antigen-presenting cells, also induces the differentiation of virgin CD4+ T cells into Th1 cells, characterized by the expression of the transcription factor Tbet, responsible for controlling a gene expression program that results in the production of IL-2, IFN-γ and TNF predominantly pro-inflammatory mediators (HAMZA; BARNETT; LI, 2010). During inflammation, such TNF released after stimulation promotes the secretion of other cytokines such as IL-1β and IL-6 (SFIKAKIS *et al*., 2010). TNF-α and IL-1β have similar effects. Both are released by activated T cells and macrophages facilitate the initiation of the local immune reaction. This reaction can produce damage to the vascular endothelium and

permeability of the blood-brain barrier, thus enabling the infiltration of immune cells into the central nervous system. In addition, TNF-α and IL-1β are also secreted by activated astrocytes and microglia and promote neurodegeneration and demyelination in the central nervous system (CHOI *et al*., 2014; DONG; YONG, 2019). IL-6 acts on endothelial cells by activating the transcription factor STAT-3, allowing the expression of chemokines and the increase of ICAM-1, recruiting leukocytes to the antigen site, which intensifies inflammation (KISHIMOTO, 2010; HIRANO, 2020). Such a pro-inflammatory cytokine is the main inducer of acute phase liver proteins secreted by neutrophils, monocytes and activated macrophages. (GOAT *et al.,* 2012; SCHMIDT-ARRAS; ROSE-JOHN, 2016). In addition, IL-6 acts on both the innate immune response and the adaptive immune response. In the innate immune response, IL-6 is readily synthesized by myeloid cells, such as macrophages and dendritic cells, after recognition of pathogens through Toll-like receptors (TLRs) at the site of infection or tissue injury. In the adaptive immune response, IL-6 induces the differentiation of B lymphocytes into plasma cells capable of producing antibodies. In combination with TGF-β, IL-6 also promotes the differentiation of Th17 cells, which produce the pro-inflammatory cytokine IL-17 (CIOFANI *et al*., 2012). Regarding excessive IL-6 production, an increase in the Th17/Treg ratio results in disruption of immune tolerance, leading to autoimmune diseases (KANG *et al*., 2019; GARBERS *et al*., 2018). Thus, several therapeutic agents are being evaluated to inhibit the cytokine itself or targets associated with its signaling pathway (GARBERS *et al*., 2018; KANG *et al*., 2019). Finally, the cytokine IL-6 is known to be involved in the inflammation of the central nervous system and pathogenesis of experimental autoimmune encephalomyelitis directly, by activating microglia and astrocytes, or indirectly, promoting the differentiation and expansion of Th17 cells (KISHIMOTO, 2010; NARAZAKI; KISHIMOTO, 2018). In mice genetically deficient in IL-6, it was not possible to induce experimental autoimmune encephalomyelitis, thus showing the relevance of IL-6 in the development of the disease (SERADA *et al*., 2008).

In addition to IL-6, IL-1 and IL-23 promote the differentiation of virgin CD4+ T cells into Th17 cells, and IL-23 may be the most important for the proliferation and maintenance of Th17 cells, whose development is dependent on the transcription factors RORγt and STAT3 (ABBAS; LICHTMAN; PILLAI, 2019). Currently, it is known that, after the adoptive transfer of IL-23-polarized T cells to virgin hosts, autoimmune encephalomyelitis is identified with a clinical picture of ascending paralysis associated with neutrophil-rich lesions and granulocytic colony-stimulating factor (G-CSF), which reveals the role of IL-23 in the pathophysiology of the model (KROENKE *et al*., 2008). TGF-β, an anti-inflammatory cytokine, in the presence of inflammation mediators such as IL-1 and IL-6, also induces the formation of Th17 cells, with an inflammatory character (ABBAS; LICHTMAN; PILLAI, 2019).

The actions of Th17 cells are primarily controlled by IL-17, with the aid of interleukin-22 (IL-22) and interleukin-21 (IL-21). IL-17 stimulates the generation of neutrophils through the production of granulocytic colony-stimulating factor (G-CSF), in addition to mediating the recruitment of neutrophils and monocytes, as well as the production of antimicrobial substances (ABBAS; LICHTMAN; PILLAI, 2019). Although its mechanisms of action in central nervous system inflammation are not elucidated, it is known that IL-17 is essential in the development of experimental autoimmune encephalomyelitis (KANG *et al*., 2010). IL-22, in turn, also secreted by NK cells and innate lymphoid cells, acts in the maintenance of epithelial integrity, although it contributes to inflammation through epithelial production of chemokines, and may be involved in tissue injury. Finally, IL-21, produced by activated TCD4+ cells, activates B cells in the germ centers, induces the differentiation of Th17 cells and amplifies the proliferation, differentiation and effector function of NK cells and CD8+ T cells (ABBAS; LICHTMAN; PILLAI, 2019).

The relevance of regulatory T cells (Treg cells) in the pathogenesis of experimental autoimmune encephalomyelitis is also highlighted, considering that the adoptive transfer of Treg cells from control mice to mice induced by MOG or PLP prevents the onset and progression of the disease (KOHM *et al*., 2002). Such lymphocytes are considered a subset of TCD4+ cells that is responsible for modulating immunity, maintaining tolerance against autoantigens, and preventing autoimmunity. They are formed after recognition of their own antigens in the thymus and peripheral lymphoid organs. These regulatory lymphocytes, if they come from the thymus, are called natural Treg cells, and if they come from peripheral lymphoid organs, they are called adaptive or inducible Treg cells. Natural Treg cells express CD4 and CD25 coreceptors and have development and immunotolerance dependent on the nuclear transcription factor Foxp3. Such regulatory lymphocytes of CD4+CD25+FOXP3+ profile are producers of IL-10, whose action is anti-inflammatory (ADEEGBE *et al*., 2006; DARGAHI *et al*., 2017). IL-10 is a cytokine involved in modulating innate and adaptive immunity and is an interleukin secreted by subtype 2 helper T cells (Th2 cells) (TRINCHIERI, 2007), although other immune cells are able to secrete it (SUN *et al.,* 2021). Previous studies show the importance of IL-10 action in the control of experimental autoimmune encephalomyelitis, due to its immunoregulatory effect. IL-10 inhibits the production of a wide variety of inflammation mediators produced by T cells, affecting antigen presentation and co-stimulation mediated by antigen-presenting cells, which are critical to the cellular immune response, thus increasing IL-10 leads to a significant reduction in disease severity (BAI *et al*., 2018). IL-12 and TNF are examples of pro-inflammatory cytokines inhibited by the anti-inflammatory activity of the cytokine IL-10 (KWILASZ *et al*., 2015; SUN *et al*., 2021).

In summary, it is recognized that the mechanism of myelin destruction in experimental autoimmune encephalomyelitis is the Th1-profile immune response, involving CD4+ and CD8+ T lymphocytes, activated macrophages, and antimyelin antibodies that activate complement and promote

phagocytosis via opsonization (ZIEMSSEN; ZIEMSSEN, 2005). Th17 cells, on the other hand, represent an essential link to the neurodegenerative processes found in experimental autoimmune encephalomyelitis, considering that, in neuroectodermal cells (neurons, astrocytes and oligodendrocytes), the deletion of Act1, a crucial component in IL-17 signaling, results in attenuation of the severity of the disease, and that, in Act1-deficient mice, Th17 cells, despite maintaining the ability to infiltrate the central nervous system, fail to recruit lymphocytes, macrophages and neutrophils (KANG *et al*., 2010).

In this chapter, we review the historical context, definition, etiology, pathophysiology, clinical manifestations, diagnosis and treatment of multiple sclerosis, an autoimmune disease whose impact on the quality of life of the sick is profound. In parallel, we address aspects about the timeline, induction, evolutionary course and immunogenesis of the most studied model for the investigation of the nuances of multiple sclerosis, experimental autoimmune encephalomyelitis, correlating the similarities and differences between both.

Clearly, it is noted that the advances attributed to the experimental autoimmune encephalomyelitis models for science are clear and have enabled the knowledge of the immunopathogenesis of multiple sclerosis, in addition to enabling the development of treatments for the disease. However, experimental autoimmune encephalomyelitis models are not without limitations. Previous studies have shown in histopathological analysis the presence of infiltrates in the spinal cord and brain of sick animals (PIAO *et al*., 2007; AHARONI *et al*., 2021). However, many classical experimental models affect the spinal cord but not the brain, in addition to being centered on CD4+ T cells, while today the substantiality of CD8+ T cells in autoimmunity-mediated inflammation of the central nervous system is already recognized. It is also common for the induction of experimental autoimmune encephalomyelitis to result in extensive tissue injury (including neurons and axons), rather than just demyelination. Finally, unfortunately, there is still a lack of experimental models representative of the PP phenotype of multiple sclerosis (LINKER; LEE, 2009). Therefore, it is essential to improve the models of experimental autoimmune encephalomyelitis, in order to provide an even more reliable approach to multiple sclerosis with regard to pathophysiology, histopathology, forms of presentation and clinical presentations, so that, then, scientific investigations are safer and more accurate.

REFERENCES

ABBAS, A. K. LICHTMAN, A. H. PILLAI, S. **Imunologia Celular e Molecular**. 9 ed. GEN Guanabara Koogan, 2019.

ABREU, P. *et al*. Esclerose Múltipla: epidemiologia, etiopatogenia, fisiopatologia e diagnóstico diferencial Multiple Sclerosis epidemiology, ethiopathogenesis, physiopathology and differential diagnosis. **Sociedade Portuguesa de Neurologia**, v. 2, n. 1, p. 5-14, nov. 2012.

ADEEGBE, D. *et al*. Cutting Edge: Allogeneic CD4+CD25+Foxp3+ T Regulatory Cells Suppress Autoimmunity while Establishing Transplantation Tolerance. **The Journal of Immunology**, v. 176, n. 12, p. 7149–7153, 2 jun. 2006.

ADELMANN, M. *et al*. The N-terminal domain of the myelin oligodendrocyte glycoprotein (MOG) induces acute demyelinating experimental autoimmune encephalomyelitis in the Lewis rat. **Journal of Neuroimmunology**, v. 63, n. 1, p. 17–27, dez. 1995.

AHARONI, R. *et al*. Titration of the myelin oligodendrocyte glycoprotein (MOG) - induced experimental autoimmune encephalomyelitis (EAE) model. **Journal of Neuroscience Methods**, p. 108999, mar. 2021.

AITKEN, M. *et al*. Medicines Use and Spending in the U.S.: A Review of 2015 and Outlook to 2020. Tampa: **Institute for Healthcare Informatics**, 2016.

ALONSO, A. HERNÁN, M. Temporal trends in the incidence of multiple sclerosis: a systematic review. **Neurology**, v. 71, n. 129, p. 129, 2008.

AL-OMAISHI, J. BASHIR, R. GENDELMAN, H. E. The cellular immunology of multiple sclerosis. **Journal of Leukocyte Biology**, v. 65, n. 4, p. 444-452, 1999.

ANDLAUER, T. F. M. *et al*. Novel multiple sclerosis susceptibility loci implicated in epigenetic regulation. **Science Advances**, v. 2, n. 6, 3 jun. 2016.

ARRAMBIDE, G. TINTORE, M.; MONTALBAN, X. Oligoclonal bands do not represent dissemination in time in the 2017 revisions to the McDonald criteria. **Multiple Sclerosis Journal**, v. 25, n. 12, p. 1690–1691, 16 maio 2019.

ASCHERIO, A. MUNGER, K. L. Epidemiology of Multiple Sclerosis: From Risk Factors to Prevention-An Update. **Seminars in neurology**, v. 36, n. 2, p. 103-14, Abr 2016.

BAI, X.-Y. *et al*. Tetramethylpyrazine ameliorates experimental autoimmune encephalomyelitis by modulating the inflammatory response. **Biochemical and Biophysical Research Communications**, v. 503, n. 3, p. 1968–1972, set. 2018.

BARBUGIANI, L. H. S. Os limites ao comércio de produtos farmacêuticos. **Revista de Direito Sanitário**, v. 15, p. 126, 2015.

BAR-OR, A. LI, R. Cellular immunology of relapsing multiple sclerosis: interactions, checks, and balances. **The Lancet Neurology**, v. 20, n. 6, p. 470–483, jun. 2021.

BATOULIS, H. *et al*. Experimental autoimune encephalomyelitis – achievements and prospective advances. **Acta Pathologica, Microbiologica Et Immunologica Scandinavica**, v. 119, p. 819-830, 2011.

BAXTER, D. Active and passive immunity, vaccine types, excipients and licensing. **Occupational Medicine**, v. 57, n. 8, p. 552–556, 28 nov. 2007.

BAYER. BAYER S.A. Betaferon® beta interferon 1b, 2016. Bula de remédio.
BECHER, B. SEGAL, B. M. TH17 cytokines in autoimmune neuro-inflammation. **Current Opinion in Immunology**, v. 23, n. 6, p. 707–712, dez. 2011

BECHER, B. SPATH, S. GOVERMAN, J. Cytokine networks in neuroinflammation. **Nat Rev Immunol** v. 17, p. 49–59, 2017.

BERNARD, C. C. A. *et al*. Myelin oligodendrocyte glycoprotein: a novel candidate autoantigen in multiple sclerosis. **Journal of Molecular Medicine**, v. 75, p. 77–88, 1997.

BIERHANSL, L. *et al*. Thinking outside the box: non-canonical targets in multiple sclerosis. **Nature Reviews Drug Discovery**, v. 21, n. 8, p. 578–600, 6 jun. 2022.

BIOGEN. Brasil Produtos Farmacêuticos Ltda. AVONEX® betainterferona 1, 2017. Bula de remédio.

BIOGEN. Brasil Produtos Farmacêuticos Ltda. TYSABRI® natalizumabe, 2018. Bula de remédio.
BIRMPILI, D. *et al*. The Translatability of Multiple Sclerosis Animal Models for Biomarkers Discovery and Their Clinical Use. **International Journal of Molecular Sciences**, v. 23, n. 19, p. 11532, 29 set. 2022.

BJELOBABA, I. *et al*. Animal models of multiple sclerosis: Focus on experimental autoimune encephalomyelitis. **J Neuro Res**, p. 1-22, 2018.

BLOZIK, E. *et al*. Epidemiology and costs of multiple sclerosis in Switzerland: an analysis of health-care claims data, 2011-2015. **Neuropsychiatr Dis Treat**, v.1, n. 13, p. 2737-2745, 2017.

BODE, J. G. *et al*. Hepatic acute phase proteins – Regulation by IL-6- and IL-1-type cytokines involving STAT3 and its crosstalk with NF-κB-dependent signaling. **European Journal of Cell Biology**, v. 91, n. 6-7, p. 496–505, jun. 2012.
BRAIN, R. Dickensian diagnoses. **BMJ**, v. 2, p. 1553, 1955.

BRASIL. Adesão ao tratamento para esclerose múltipla com terapias de primeira linha: análise longitudinal retrospectiva. **Jornal de Assistência Farmacêutica e Farmacoeconomia**, 2017.

BRASIL. Ministérios da Saúde. Secretaria de Atenção Especializada à Saúde Secretaria de Ciência, Tecnologia e Insumos Estratégicos em Saúde. **Protocolo Clínico e Diretrizes Terapêuticas da Esclerose Múltipla**. Brasília, 2021.

BRUCK, W. *et al*. Monocyte/macrophage differentiation in early multiple sclerosis lesions. **Annals of Neurology**, v. 38, n. 5, p. 788–796, 1995.

BUTCHER, M. J. ZHU, J. Plasticity and functionality of Th17 subsets in EAE. **The Journal of Immunology**, v. 200, n. 1 supl., p. 163.20–163.20, mai. 2018.

CANTO, E. OKSENBERG, J. R. Multiple sclerosis genetics. **Multiple Sclerosis Journal,** v. 24, n. 1, p. 75-79, Jan 2018.

CHARCOT, J. M. Ouevres complètes de J.-M. Charcot. Leçons sur les maladies du système nerveux recueilles et publiées par Bourneville, Tome 1. Paris: **Bureau du Progres Medical and A Delahaye**, 1886.

CHENG, W. CHEN, G. Chemokines and Chemokine Receptors in Multiple Sclerosis. **Mediators of Inflammation**, v. 2014, p. 1–8, 2014.

CHOI, S. S. *et al*. Human Astrocytes: Secretome Profiles of Cytokines and Chemokines. **PLoS ONE**, v. 9, n. 4, p. e92325, 1 abr. 2014

CIOFANI, M. *et al*. A Validated Regulatory Network for Th17 Cell Specification. **Cell**, v. 151, n. 2, p. 289–303, out. 2012.
COETZEE, T. THOMPSON, A. J. Atlas of MS 2020: Informing global policy change. **Multiple Sclerosis Journal**, v. 26, n. 14, p. 1807–1808, 11 nov. 2020.

COMPSTON, A. COLES, A. Multiple sclerosis. **The Lancet**, v. 372, n. 9648, p. 1502–1517, 2008.

CONTARINI, G. GIUSTI, P. SKAPER, S. D. Active Induction of Experimental Autoimmune Encephalomyelitis in C57BL/6 Mice. **Neurotrophic Factors**, p. 353–360, 9 dez. 2017.

CORREALE, J. FAREZ, M. F. Smoking worsens multiple sclerosis prognosis: two different pathways are involved. **Journal of Neuroimmunology.** v. 281, p. 23-34, abr. 2015.

DARGAHI, N. *et al*. Multiple Sclerosis: Immunopathology and Treatment Update. **Brain sciences**, v. 7, n. 7, p. 78, 2017.

DEGLIANTONI, G. *et al*. Inhibition of bone marrow colony formation by human natural killer cells and by natural killer cell-derived colony-inhibiting activity. **Journal of Experimental Medicine**, v. 161, n. 5, p. 1152–1168, 1 maio 1985.

DENDROU, C. A. FUGGER, L. FRIESE, M. A. Immunopathology of multiple sclerosis. **Nature Reviews Immunology**, v. 15, n. 9, p. 545–558, 7 ago. 2015.

DE ROSBO N. K. MENDEL, I. BEN-NUN, A. Chronic relapsing experimental autoimmune encephalomyelitis with a delayed onset and an atypical clinical course, induced in PL/J mice by myelin oligodendrocyte glycoprotein (MOG)-derived peptide: preliminary analysis of MOG T cell epitopes. **Journal of Immunology**, v. 25, p. 985–993, 1995.

DIAS, D. S. *et al.* Copaiba oil suppresses inflammatory cytokines in splenocytes of C57Bl/6 mice induced with experimental autoimmune encephalomyelitis (EAE). **Molecules**. v. 19, p. 12814-19826, 2014.

DONG, Y. YONG, V. W. When encephalitogenic T cells collaborate with microglia in multiple sclerosis. **Nature reviews. Neurology**, v. 15, p. 704–717, 2019.

DOS SANTOS, A. C. *et al*. CCL2 and CCL5 mediate leukocyte adhesion in experimental autoimmune encephalomyelitis—an intravital microscopy study. **Journal of Neuroimmunology**, v. 162, n. 1-2, p. 122–129, mai. 2005.

DUFFY, S. S. LEES, J. G; MOALEM-TAYLOR, G. The contribution of immune and glial cell types in experimental autoimmune encephalomyelitis and multiple sclerosis. **Multiple Sclerosis International**, 2014.

ELICES, M. J. *et al*. VCAM-1 on activated endothelium interacts with the leukocyte integrin VLA-4 at a site distict from the VLA-4/fibronectin binding site. **Cell Amsterdam**, v. 60, p. 577–584, 1990.

ENGELHARDT, B. KAPPOS, L. Natalizumab: Targeting α4-Integrins in Multiple Sclerosis. **Neurodegenerative Diseases**, v. 5, p. 16–22, 2008.

EPPS, H. L. V. Thomas Rivers and the EAE model. **The Journal of Experimental Medicine**, 2005.

FERRE, L. *et al*. Basal vitamin D levels and disease activity in multiple sclerosis patients treated with fingolimod. **Neurological Sciences,** v. 39, n. 8, p. 1467-1470, ago. 2018.

FILIPPI, M. ROCCA, M. A. Multiple Sclerosis. **White Matter Diseases**, p. 1–35, 2020.

FONTES, L. B. A. *et al*. Immunomodulatory effects of licochalcone A on experimental autoimmune encephalomyelitis. **The Journal of pharmacy and pharmacology**, v. 66, p. 886–894, 2014.

FONTES, L. B. A. *et al*. β-Caryophyllene ameliorates the development of experimental autoimmune encephalomyelitis in C57BL/6 mice. **Biomedicine & pharmacotherapy**, v. 91, p. 257-264, 2017.

FRAGOSO, Y. D. ELSO, F. G. CARRA, A. Differential diagnosis of multiple sclerosis in Latin America. **Mult Scler J Exp Transl Clin.** v. 3, n. 3, p. 2055217317714279, Jul-Sep 2017.

FRANKLIN, R. J. M. FFRENCH-CONSTANT, C. Remyelination in the CNS: From biology to therapy. **Nature Reviews Neuroscience**, v. 9, n. 11, p. 839–855, 2008.

FRISULLO, G. et al. Circulating CD8+CD56−perforin+ T cells are increased in multiple sclerosis patients. **Journal of Neuroimmunology**, v. 240-241, p. 137–141, dez. 2011.

FROHMAN, E. M.; RACKE, M. K.; RAINE, C. S. Multiple sclerosis-the plaque and its pathogenesis. **Journal of Medicine**, v. 354, n. 9, p. 942–955, 2006.

GAJOFATTO, A. BENEDETTI, M. D. Treatment strategies for multiple sclerosis: When to start, when to change, when to stop. **World Journal of Clinical Cases**, v. 3, p. 545, 2015.

GANDRA, A. Governo distribui medicação de alto custo para esclerose múltipla. **Agência Brasil**, 2019.

GARBERS, C. *et al*. Interleukin-6: designing specific therapeutics for a complex cytokine. **Nature Reviews Drug Discovery**, v. 17, n. 6, p. 395–412, 4 maio 2018.

GENZYME A SANOFI COMPANY. AUBAGIO® teriflunomida. 2016.

GHOLAMZAD, M. *et al*. A comprehensive review on the treatment approaches of multiple sclerosis: currently and in the future. **Inflammation Research**, v. 68, n. 1, p. 25–38, 3 set. 2018.

GLATIGNY, S. BETTELLI, E. Experimental Autoimmune Encephalomyelitis (EAE) as Animal Models of Multiple Sclerosis (MS). **Cold Spring Harbor Perspectives in Medicine**, v. 8, n. 11, p. a028977, 8 jan. 2018.

GONSETTE, R. E. Self-tolerance in multiple sclerosis. **Acta Neurologica Belgica**, v. 112, n. 2, p. 133–140, 24 mar. 2012.

GOVERMAN, J. Autoimune T cell responses in the central nervous system. **Nature Reviews Immunology**, v. 9, n. 6, p. 393-407, jun. 2009.

HAAS, J. *et al*. Prevalence of Newly Generated Naive Regulatory T Cells (Treg) Is Critical for Treg Suppressive Function and Determines Treg Dysfunction in Multiple Sclerosis. **The Journal of Immunology**, v. 179, n. 2, p. 1322–1330, 15 jul. 2007.

HAMZA, T. BARNETT, J. B. LI, B. Interleukin 12 a Key Immunoregulatory Cytokine in Infection Applications. **International Journal of Molecular Sciences**, v. 11, n. 3, p. 789–806, 26 fev. 2010.

HARTUNG, H.-P. *et al*. Diagnosis of multiple sclerosis: revisions of the McDonald criteria 2017 - continuity and change. **Current opinion in neurology**, v. 32, n. 3, p. 327–337, 2019.

HASSELMANN, J. P. C. *et al*. Consistent induction of chronic experimental autoimmune encephalomyelitis in C57BL/6 mice for the longitudinal study of pathology and repair. **Journal of neuroscience methods**, v. 284, p. 71–84, 1 jun. 2017.

HAUSER, S. L. CREE, B. A. C. Treatment of Multiple Sclerosis: A Review. **The American Journal of Medicine**, v. 133, n. 12, p. 1380-1390.e2, dez. 2020.

HELLINGS, N. *et al*. T-Cell Reactivity to Multiple Myelin Antigens in Multiple Sclerosis Patients and Healthy Controls. **Journal of Neuroscience Research**, v. 63, n. 3, p. 203-302, 2001.

HIRANO, T. IL-6 in inflammation, autoimmunity and cancer. **International Immunology**, v. 33, n. 3, p. 127–148, 18 dez. 2020.

HORGA, A. TINTORÉ, M. Natalizumab for relapsing-remitting multiple sclerosis. **Neurología**, v. 2011, p. 357–368, 2011.

HUNTEMANN, N. *et al*. An optimized and validated protocol for inducing chronic experimental autoimmune encephalomyelitis in C57BL/6J mice. **Journal of Neuroscience Methods**, v. 367, p. 109443, fev. 2022.
IFERGAN, I. *et al*. The blood-brain barrier induces differentiation of migrating monocytes into Th17-polarizing dendritic cells. **Brain: A Journal of Neurology**, v. 131, n. Pt 3, p. 785– 799, 1 mar. 2008.

JAHAN-ABAD, A. J. *et al*. Serum pro-inflammatory and anti-inflammatory cytokines and the pathogenesis of experimental autoimmune encephalomyelitis. **Neuropathology**, 10 nov. 2019.

JAKIMOVSKI, D. *et al*. Lifestyle-based modifiable risk factors in multiple sclerosis: review of experimental and clinical findings. **Neurodegenerative Disease Management**, v. 9, n. 3, p. 149–172, jun. 2019.

JONES, J. L. COLES, A. New treatment strategies in multiple sclerosis. **Experimental Neurology**, v. 225, p. 34–39, 2010.

JURGA, A. M. PALECZNA, M. KUTER, K. Z. Overview of General and Discriminating Markers of Differential Microglia Phenotypes. **Frontiers in Cellular Neuroscience**, v. 14, 6 ago. 2020.

KANG, S. *et al*. Targeting Interleukin-6 Signaling in Clinic. **Immunity**, v. 50, n. 4, p. 1007–1023, abr. 2019.

KANG, Z. *et al*. Astrocyte-Restriced Ablation of Interleukin-17-Induced Act1-Mediated Signaling Ameliorates Autoimmune Encephalomyelitis. **Immunity**, v. 32, p. 414-425, 2010.

KIPP, M. *et al*. Multiple sclerosis animal models: a clinical and histopathological perspective. **Brain pathology,** v. 27, n. 2, p. 123–137, 2017.

KISHIMOTO, T. IL-6: from its discovery to clinical applications. **International Immunology**, v. 22, n. 5, p. 347–352, 21 abr. 2010.

KLEFBECK, B. NEDJAD, J. Effect of inspiratory muscle training in patients with multiple sclerosis. **Archives of Physical Medicine and Rehabilitation**, v. 84, n. 7, p. 994-999, 2003.

KLOTZ, L. *et al*. Teriflunomide treatment for multiple sclerosis modulates T cell mitochondrial respiration with affinity-dependent effects. **Science Translational Medicine**, v. 11, 2019.

KNUTH, A. K. *et al*. Interferons Transcriptionally Up-Regulate MLKL Expression in Cancer Cells. **Neoplasia**, p. 74–81, 2019.

KOBELT, G. *et al*. Burden and cost of multiple sclerosis in Brazil. **PLOS ONE**, v. 14, n. 1, p. e0208837, 23 jan. 2019.

KOCH-HENRIKSEN, N. SØRENSEN, P. S. The changing demographic pat tern of multiple sclerosis epidemiology. **Lancet Neurolology**, v. 9, p. 5, 2010.

KOHM, A. P. *et al*. Cutting Edge: CD4+CD25+ Regulatory T Cells Suppress Antigen-Specific Autoreactive Immune Responses and Central Nervous System Inflammation During Active Experimental Autoimmune Encephalomyelitis. **The Journal of Immunology**, v. 169, n. 9, p. 4712–4716, 1 nov. 2002.

KORNBERG, M. D. *et al*. Dimethyl fumarate targets GAPDH and aerobic glycolysis to modulate immunity. **Science**, v. 360, p. 449–453, 2018.

KROENKE, M. A. *et al*. IL-12- and IL-23-modulated T cells induce distinct types of EAE based on histology, CNS chemokine profile, and response to cytokine inhibition. **J Exp Med**, v. 205, n. 7, p. 1535-1541, 2008.

KROEPFL, J. F. *et al*. Investigation of Myelin/Oligodendrocyte Glycoprotein Membrane Topology. **Journal of Neurochemistry**, v. 67, n. 5, p. 2219–2222, 23 nov. 2002.

KWILASZ, A. J. *et al*. The therapeutic potential of interleukin-10 in neuroimmune diseases. **Neuropharmacology**, v. 96, p. 55–69, set. 2015.

KYRAN, E. L. *et al*. Multiple pathological mechanisms contribute to hippocampal damage in the experimental autoimmune encephalomyelitis model of multiple sclerosis. **NeuroReport**, v. 29, n. 1, p. 19–24, 3 jan. 2018.

LALIVE, P. H. *et al*. Antibodies to native myelin oligodendrocyte glycoprotein are serologic markers of early inflammation in multiple sclerosis. **Proc. Natl. Acad. Sci. U S A.**, v. 103(7), p. 2280- 2285, 2006.

LANDTBLOM, A. *et al*. O primeiro caso clínico de esclerose múltipla: Augustus d'Este (1794–1848). **Neurological Sciences**, v. 31, p. 29–33, 2010

LASSMANN, H. Multiple Sclerosis Pathology. **Cold Spring Harbor Perspectives in Medicine**, v. 8, n. 3, p. a028936, 22 jan. 2018.

LASSMANN, H. Targets of therapy in progressive MS. **Multiple Sclerosis Journal**, v. 23, n. 12, p. 1593–1599, out. 2017.

LEBRUN-FRENAY, C. *et al*. Radiologically Isolated Syndrome: 10-Year Risk Estimate of a Clinical Event. **Annals of Neurology**, v. 88, n. 2, p. 407–417, 29 jun. 2020.

LIBLAU, R. S. SINGER, S. M. MCDEVITT, H. O. Th1 and Th2 CD4+ T cells in the pathogenesis of organ-specific autoimmune diseases. **Immunology Today**, v. 16, n. 1, p. 34– 38, jan. 1995.

LININGTON, C. *et al*. Induction of persistently demyelinated lesions in the rat following the repeated adoptive transfer of encephalitogenic T cells and demyelinating antibody. **Journal of Neuroimmunology**, v. 40, n. 2-3, p. 219–224, out. 1992.

LININGTON, C. *et al*. T cells specific for the myelin oligodendrocyte glycoprotein mediate an unusual autoimmune inflammatory response in the central nervous system. **European Journal of Immunology**, v. 23, n. 6, p. 1364–1372, jun. 1993.

LINKER, R. A. LEE, D-H. Models of autoimune demyelination in the central nervous system: on the way to translational medicine. **Exp Transl Stroke Med**, v. 1, n. 5, 2009.

LINNINGTON, C. WEBB, M. WOODHAMS, P. L. A novel myelin-associated glycoprotein defined by a mouse monoclonal antibody. **Journal of Neuroimmunology**, v. 6, n. 6, p. 387–396, set. 1984.

LO, L. M. P. *et al*. Estimar a contribuição relativa das comorbidades na previsão da qualidade de vida relacionada à saúde de pessoas com esclerose múltipla. **Journal of Neurology**, v. 268, p. 569–581, 2021.

LOPES, E. R. *et al*. Bogliolo Patologia. 4 ed. Rio de Janeiro: **Guanabara Koogan**, 1987.

LUBLIN, F. D. *et al*. Defining the clinical course of multiple sclerosis: The 2013 revisions. **Neurology**, v. 83, n. 3, p. 278–286, 28 maio 2014.

LUCCHINETTI, C. *et al*. Heterogeneity of multiple sclerosis lesions: implications for the pathogenesis of demyelination. **Annals of Neurology**, v. 47, p. 707–717, 2000.

LUTTEROTTI, A. BERGER, T.; REINDL, M. Biological markers for multiple sclerosis. **Current Medicinal Chemistry**, 2007.

MARTIN, R. MCFARLAND, H. F. MCFARLIN, D. E. Immunological Aspects of Demyelinating Diseases. **Annual Review of Immunology**, v. 10, n. 1, p. 153-187, 1992.

MASVEKAR, R. *et al*. Cerebrospinal fluid biomarkers link toxic astrogliosis and microglial activation to multiple sclerosis severity. **Multiple Sclerosis and Related Disorders**, v. 28, p. 34–43, fev. 2019.

MCDONALD, W. I. et al. Recommended diagnostic criteria for multiple sclerosis: Guidelines from the international panel on the diagnosis of multiple sclerosis. **Annals of Neurology**, v. 50, n. 1, p. 121–127, 2001.

MCGINLEY, A. M. *et al*. Th17 cells, γδ T cells and their interplay in EAE and multiple sclerosis. **Journal of Autoimmunity**, v. 87, p. 97–108, fev. 2018.

MILLER, C. H. T. MAHER, S. G. YOUNG, H. A. Clinical Use of Interferon-γ. **Annals of the New York Academy of Sciences**, v. 1182, p. 69–79, 1 dez. 2009.

MILLER, S. D. KARPUS, W. J. DAVIDSON, T. S. Experimental Autoimmune Encephalomyelitis in the Mouse. **Curr Protoc Immunol**, 2007.

MILO, R. MILLER, A. Revised diagnostic criteria of multiple sclerosis. **Autoimmunity Reviews**, v. 13, n. 4–5, p. 518–524, 2014.

MILOVANOVIC, J. *et al*. Interleukin-17 in Chronic Inflammatory Neurological Diseases. **Frontiers in Immunology**, v. 11, 3 jun. 2020.

MOJAVERROSTAMI, S. *et al*. A Review of Herbal Therapy in Multiple Sclerosis. **Adv Pharm Bull. Pharm Bulletin**, 2018.

MOUTSIANAS, L. *et al*. Class II HLA interactions modulate genetic risk for multiple sclerosis. **Nat Genet**, 47, n. 10, p. 1107-1113, 2015.

MUNGER, K. L. *et al*. Serum 25-Hydroxyvitamin D Levels and Risk of Multiple Sclerosis. **JAMA**, v. 296, n. 23, p. 2832, 20 dez. 2006.

NARAZAKI, M. KISHIMOTO, T. The Two-Faced Cytokine IL-6 in Host Defense and Diseases. International Journal of Molecular Sciences, v. 19, n. 11, p. 3528, 9 nov. 2018.

NOURBAKHSH, B. MOWRY, E. M. Multiple Sclerosis Risk Factors and Pathogenesis. **CONTINUUM: Lifelong Learning in Neurology**, v. 25, n. 3, p. 596–610, jun. 2019.

NOVARTIS. Biociências LTDA. GILENYA® cloridrato de fingolimode, 2015. Bula de remédio.
NOVO, A. M. BATISTA, S. Multiple Sclerosis: Implications of Obesity in Neuroinflammation. **Adv Neurobiol**. v. 19, p. 191-210, 2017.

OLECHOWSKI, C. J. *et al*. A diminished response to formalin stimulation reveals a role for the glutamate transporters in the altered pain sensitivity of mice with experimental autoimmune encephalomyelitis (EAE). **Pain**, v. 149, n. 3, p. 565–572, jun. 2010.

OLIVEIRA, E. M. L. SOUZA, N. A. Esclerose Múltipla. **Rev. Neurociências**, v. 6, n. 3, p. 114-118, 1998.

PASSOS, G. R. D. *et al*. Th17 Cells Pathways in Multiple Sclerosis and Neuromyelitis Optica Spectrum Disorders: Pathophysiological and Therapeutic Implications. **Mediators of Inflammation**, v. 2016, p. 1–11, 2016.

PEREIRA, A. B. C. N. G. *et al*. Prevalence of multiple sclerosis in Brazil: A systematic review. **Multiple Sclerosis and Related Disorders**, v. 4, p. 572–579, 2015.

PEREIRA, D. S. N. B. *et al*. Animais como modelos experimentais nos cursos de graduação na área da saúde: revisão sistemática. **Revista Eletrônica Acervo Saúde**, 2020.

PETZOLD, A. Neurite óptica: outro diagnóstico de Dickens. **Neuro - Ophthalmology**, p. 247– 50, 2013.

PIAO, W.-H. *et al.* Therapeutic Effect of Anthracene-Based Anticancer Agent Ethonafide in an Animal Model of Multiple Sclerosis. **The Journal of Immunology**, v. 179, n. 11, p. 7415– 7423, 1 dez. 2007.

PICCIO, L. *et al*. Molecular Mechanisms Involved in Lymphocyte Recruitment in Inflamed Brain Microvessels: Critical Roles for P-Selectin Glycoprotein Ligand-1 and Heterotrimeric Gi-Linked Receptors. **Journal of Immunology**, v. 168, n. 4, p. 1940–1949, 2002.

PLATTEN, M. STEINMAN, L. Anti-inflammatory strategies for the treatment of multiple sclerosis – tryptophan catabolites may hold the key. Amsterdam: **Drug Discovery Today: Therapeutic Strategies**, v. 33, p. 401–408, 2006.

RACKE, M. K. LOVETT-RACKE, A. E. Glatiramer Acetate Treatment of Multiple Sclerosis: An Immunological Perspective. **The Journal of Immunology**, v. 186, n. 4, p. 1887–1890, 15 fev. 2011.

REDER, A. T. FENG, X. How Type I Interferons Work in Multiple Sclerosis and Other Diseases: Some Unexpected Mechanisms. **Journal of Interferon & Cytokine Research**, v. 34, p. 589–599, 2014.

REDFERN, J. S. Immunopathophysiologic basis of multiple sclerosis and implications for therapy-a narrative review. **Pharmacy & Pharmacology International Journal**, v. 9, n. 6, p. 263–271, 21 dez. 2021.

REZENDE, P. A. ARRUDA, W. O. Imunopatologia da Esclerose Múltipla. **Revista Brasileira de Neurologia**, v. 34, n. 3, p. 97-103, jun. 1998.

ROBINSON, A. P. *et al*. Chapter 8 - The experimental autoimune encephalomyelitis (EAE) model of MS: utility for understanding disease pathophysiology and treatment. In: GOODING, D. S. Handbook of Clinical Neurology. **Elsevier**, v. 122, p. 173-189, 2014.

SALAZAR, I. L. *et al*. Posttranslational modifications of proteins are key features in the identification of CSF biomarkers of multiple sclerosis. **Journal of Neuroinflammation**, v. 19, n. 1, 8 fev. 2022.

SCHULZE-TOPPHOFF, U. *et al*. Dimethyl fumarate treatment induces adaptive and innate immune modulation independent of Nrf2. **Proceedings of the National Academy of Sciences**, v. 113, p. 4777–4782, 2016.

SCOLDING, N. J. FRANKLIN, R. J. M. Axon loss in multiple sclerosis. **Lancet**, v. 352, p. 340-341, 1998.

SCHMIDT-ARRAS, D. ROSE-JOHN, S. IL-6 pathway in the liver: From physiopathology to therapy. **Journal of Hepatology**, v. 64, n. 6, p. 1403–1415, jun. 2016.

SERADA, S. *et al*. IL-6 blockade inhibits the induction of myelin antigen-specific Th17 cells and Th1 cells in experimental autoimmune encephalomyelitis. **Proceedings of the National Academy of Sciences**, v. 105, n. 26, p. 9041–9046, jul. 2008.

SFIKAKIS, P. P. *et al.* **A primeira década de antagonistas biológicos do TNF na prática clínica**: lições aprendidas, questões não resolvidas e orientações futuras, 2010.

SILVA, A. K. G. DE PAULA, M. L. FERREIRA, A. P. Imunopatologia da encefalomielite auto-imune experimental murina mediada por linfócitos T. Juiz de Fora: **HU Revista**, v. 34, n. 3, p. 205-212, 2008.

SILVA, N. L. *et al*. Cost analysis of multiple sclerosis in Brazil: a cross-sectional multicenter study. **Bmc Health Services Research**, v. 16, p. 102–124, 2016.

SIMPSON, S. *et al*. Latitude continues to be significantly associated with the prevalence of multiple sclerosis: an updated meta-analysis. **Journal of Neurology, Neurosurgery & Psychiatry**, v. 90, n. 11, p. 1193–1200, 19 jun. 2019.

SLOANE, E. LEDEBOER, A. Anti-inflammatory cytokine gene therapy decreases sensory and motor dysfunction in experimental Multiple Sclerosis: MOGEAE behavioral and anatomical symptom treatment with cytokine gene therapy. **Brain, Behavior, and Immunity**, 2009.

SPENCER, C. M. *et al*. Reduction of CD8(+) T lymphocytes in multiple sclerosis patients treated with dimethyl fumarate. **Neurology(R) Neuroimmunology & Neuroinflammation**, v. 2, 2015.
SOBIERA, D. M. Fingolimod: A potential first-in-class oral therapy for the treatment of relapsing-remmiting multiple sclerosis. North Olmsted: **Formulary**, v. 45, ed. 8, p. 245-251, 2010.

SOLLID, L. M. Epstein-Barr virus as a driver of multiple sclerosis. **Science Immunology**, v. 7, n. 70, abr. 2022.

SOLOMON, A. J. Diagnosis, Differential Diagnosis, and Misdiagnosis of Multiple Sclerosis. **CONTINUUM: Lifelong Learning in Neurology**, v. 25, n. 3, p. 611–635, jun. 2019.

SOSPEDRA, M. MARTIN, R. IMMUNOLOGY OF MULTIPLE SCLEROSIS. **Annual Review of Immunology**, v. 23, n. 1, p. 683–747, abr. 2005.

STEFFERL, A. *et al*. Myelin oligodendrocyte glycoprotein induces experimental autoimmune encephalomyelitis in the “resistant” Brown-Norway rat: disease susceptibility is determined by MHC and MHC-linked effects on the B cell response. **J Immunol**, v. 163, n. 1, p. 40-9, 1999.

STORK, M. K. *et al*. Autoimmunity to myelin oligodendrocyte glycoprotein in rats mimics the spectrum of multiple sclerosis pathology. **Brain Pathology**, v. 8, p. 681–694, 1998.

SUN, H. *et al*. IL-10-Producing ILCs: Molecular Mechanisms and Disease Relevance. **Frontiers in Immunology**, v. 12, 29 mar. 2021.

SWANBORG, R. H. Experimental autoimmune encephalomyelitis in rodents as a model for human demyelinating disease. **Clin Immunol Immunopathol**, v. 77, n.1, p. 4-13, 1995.

TABANSKY, I. *et al*. Advancing drug delivery systems for the treatment of multiple sclerosis. **Immunologic Research**, v. 63, p. 58–69, 2015.

TEVA. TEVA Pharmaceuticals LTDA. COPAXONE (acetato de glatirâmer) ®, 2014. Bula de remédio.

THOMPSON, A. J. *et al*. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. **The Lancet Neurology**, v. 17, n. 2, p. 162–173, fev. 2018.

TOBORE, O. T. Oxidative/Nitroxidative Stress and Multiple Sclerosis. **Journal of Molecular Neuroscience**, v. 71, p. 506–514, 2021.

TRINCHIERI, G. Interleukin-10 production by effector T cells: Th1 cells show self-control. **Journal of Experimental Medicine**, v. 204, n. 2, p. 239–243, 12 fev. 2007.
UNPHRED, D. A. **Reabilitação neurológica**. São Paulo: Manole, 2004.

VAN KAER, L. e*t al*. Innate, innate-like and adaptive lymphocytes in the pathogenesis of MS and EAE. **Cellular & Molecular Immunology**, v. 16, n. 6, p. 531–539, 15 mar. 2019.

VIEGAS, F. C. S. **Estudo clínico-histopatológico da encefalomielite auto-imune experimental em camundongos selvagens e deficientes para a apolipoproteína-E**. 87 f. Dissertação (Mestrado em Biologia Celular) – Instituto de Ciências Biológicas, Universidade Federal de Minas Gerais, Belo Horizonte, 2009.

VOLPI, C. *et al*. Preclinical discovery and development of fingolimod for the treatment of multiple sclerosis. **Expert Opinion on Drug Discovery**, p. 1199–1212, 2019.

WALTON, C. *et al*. Rising prevalence of multiple sclerosis worldwide: Insights from the Atlas of MS, third edition. **Multiple Sclerosis Journal**, v. 26, n. 14, p. 1816–1821, 11 nov. 2020.

WAUBANT, E. *et al*. Environmental and genetic risk factors for MS: an integrated review. **Annals of Clinical and Translational Neurology**, v. 6, n. 9, p. 1905–1922, 7 ago. 2019.

WILLENBORG, D. O. Experimental Allergic Encephalomyelitis in the Lewis Rat: Studies on the Mechanism of Recovery from Disease and Acquired Resistance to Reinduction. **J Immunol**, v. 123, n. 3, p. 1145-1150, 1979.

WILLER, C. J. *et al*. Twin concordance and sibling recurrence rates in multiple sclerosis. **Proceedings of the National Academy of Sciences**, v. 100, n. 22, p. 12877–12882, 20 out. 2003.

WLODARCZYK, A. *et al*. Comparison of microglia and infiltrating CD11c+ cells as antigen presenting cells for T cell proliferation and cytokine response. **Journal of Neuroinflammation**, v. 11, n. 1, 25 mar. 2014.

WUCHERPFENNIG, K. W. *et al*. Structural alterations in peptide–MHC recognition by selfreactive T cell receptors. **Current Opinion in Immunology**, v. 21, n. 6, p. 590–595, dez. 2009.

YANG, J. **Peripheral Immune Response in Chronic Relapsing Experimental Autoimmune Encephalomyelitis in SJL mice**. 84 f. Dissertação (Mestrado em Neurociência) – Universidade de Helsinki, Finlândia, 2003.

YIN, Y. *et al*. Structure of a TCR with high affinity for self-antigen reveals basis for escape from negative selection. **The EMBO Journal**, v. 30, n. 6, p. 1137–1148, 4 fev. 2011.

ZAGON, I. S. MCLAUGHLIN, P. J. Multiple sclerosis: perspectives in treatment and pathogenesis. Brisbane, Australia: **Codon Publications**, 2017.

ZETTERBERG, H. Fluid biomarkers for microglial activation and axonal injury in multiple sclerosis. **Acta Neurologica Scandinavica**, v. 136, p. 15–17, 25 out. 2017.

ZIEMSSEN, T. ZIEMSSEN, F. The role of the humoral immune system in multiple sclerosis (MS) and its animal model experimental autoimmune encephalomyelitis (EAE). **Autoimmun Rev**, v. 4, n. 7, p. 460-7, 2005.