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ADVANCES IN THERAPEUTIC APPROACHES FOR THE TREATMENT OF MULTIPLE SCLEROSIS: CURRENT AND FUTURE PERSPECTIVES.

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Abstract

Background: multiple sclerosis (MS) is a chronic multifactorial inflammatory disease of the central nervous system (CNS), which causes demyelination and neurodegeneration, can result in severe deterioration in both physical and cognitive functions.
Objective: to describe advances in therapeutic approaches for the treatment of multiple sclerosis: current and future perspectives.
Methodology: study with a qualitative, non experimental, narrative bibliographic approach, based on the review of sources of the different scientific databases, taking into account high impact articles present in digital platforms, linked to health, such as NCBI, Scielo, Science, Sciencedirect, Dialnet, Springerlink among others. The articles used were published from 2018 onwards, in Spanish and English as a priority. The searches were carried out with the help of keywords and Boolean operators AND and OR, guaranteed better results.
Results: The literature review identified that the main therapeutic approaches used are glatiramer acetate, Interferon, Natalizumab, Fingolimod, Teriflunomide, natalizumab, fingolimod, rituximab, azathioprine, mitoxantrora, dimethylfumarate, cladribine, with different levels of efficacy. Few clinical trials were documented, which constitutes a limitation of the use of different therapeutic approaches in the management of multiple sclerosis.
Conclusions: Limited and insufficient studies and research on effectiveness and safety of therapeutic approaches in the management of multiple sclerosis are a challenge and challenge for science

Keywords: multiple sclerosis, central nervous system, therapeutic approach, diagnosis

CHAPTER 1: INTRODUCTORY FRAMEWORK

Introduction

Multiple sclerosis (MS) is a chronic demyelinating autoimmune disease of the central nervous system (CNS). It is characterized by inflammation and neuroaxonal degeneration, which causes disease relapses and increased disability in patients (1).
Multiple sclerosis has a variable and unpredictable clinical course, in severity, as well as in the evolution of symptoms. In a large part of patients the relapsing-remitting form (RRMS) develops,

which may or may not have permanent neurological deficits as well as disability, secondary progressive multiple sclerosis (SPMS) (1)
In multiple sclerosis, the areas that have been altered by the disease are responsible for the clinical manifestations presented by patients, hence, it can be said that the symptoms presented by people with this disease are unique. Therefore, the therapeutic approach must have a comprehensive approach oriented mainly to each patient individually and thus optimize the process for the well-being of the patient, including in the treatment actions that achieve better results with the patient. (2).
Therapeutically controlling the chronic progression of multiple sclerosis (MS) remains a major challenge for medical science, hence the value placed on investigating advances in therapeutic approaches to the treatment of multiple sclerosis from both current and future perspectives.

Problem statement

Multiple sclerosis (MS) is a chronic disease of the central nervous system (CNS) that causes demyelination and neurodegeneration. It is characterized by presenting a very progressive inflammatory process, this causes a deterioration within the neuronal components, and in turn, injuries within the functional systems of the brain that are the determinants for the appearance of symptoms, which are manifested through fatigue, pain, cognitive impairment, loss of balance, deficit in motor skills, constant fatigue, bladder dysfunction and spasticity. Multiple sclerosis is the leading cause of irreversible damage in young people and mainly affects women, with a ratio of 3:1 to men (3).
The disease in question has been studied in different parts of the world, finding that it occurs in more than 2 million people around the world. (4). Research conducted in Spain shows a significant prevalence of this disease, with an average of 200 cases per 100,000 people. Approximately 550,000 cases have been found in Europe; and more than 2.5 million have been found worldwide. Frequently, the age at which the first signs and symptoms are observed are between 20 - 45 years, however, it has also occurred in infants and older adults. (5).
From the epidemiological perspective, this disease appeared more frequently in the United States and other countries in Europe, however, over the years, it has spread to other countries in the world, becoming a global problem. The prevalence of multiple sclerosis presents data indicating that there are 30 cases per 100,000 inhabitants considering the world population. However, with respect to the cumulative prevalence rate, a lower figure of 0.5 is reflected in Africa, likewise, in Asia there is a decrease of 8.3. However, in more recent reports, data has been published indicating a global prevalence of multiple sclerosis of 33 per 100,000 inhabitants, this suggests that there are more than 2 million people affected by multiple sclerosis in the world (WHO, 2022). These recently published data do not clearly detail the reasons for the increase in cases, being attributed to some causes such as a better detection process, better technological equipment for diagnosis or an improved system for the effectiveness of notification. (6).
The data that are handled in Mexico, show that, in 2018, more than 1200 people with symptoms of multiple sclerosis were reported, this according to the reports presented by the SIAM. All these cases were scattered throughout different parts of the country, and making a conglomerate of all of them, there is a value of 20% of the total of neurology patients, these patients being mostly female (7).
The prevalence of multiple sclerosis is low or intermediate in Latin American countries, with between 1.5-38 cases per 100,000 inhabitants reported. In Ecuador, a low prevalence is reported, being 3-5 cases per 100,000 inhabitants. The presence of this disease has been identified more frequently in cities such as Quito and Cuenca, where there is a smaller indigenous population and more white and mestizo population, which suggests the influence of European population in the presence of the disease (8).
At present, treatment options still rely heavily on disease-modifying procedures that do not treat the underlying cause, but instead attempt to suppress and improve the symptoms experienced. However, with advances in drug delivery methods and therapeutic regimen, new treatment options have emerged, capable of addressing the demyelinating process of MS. (9).
The treatment of multiple sclerosis has experienced an important advance within medical practice thanks to the development of various mechanisms, such as immune modulation, suppression that is

managed within these immune cells and enhanced sequestration of immune cells. Emerging therapies include Bruton's tyrosine kinase inhibitors that penetrate the nervous system and autologous hematopoietic stem cell transplantation. Certain treatments that target the remyelination system are also used. The steady advancement of therapy for this progressive disease is a complete challenge because of the limited efficacy of the components currently approved for inactive disease and older adults. (10).

However, the continuous advances of science and technology in the field of medicine require that health professionals, as well as scientific experts, work in cooperation in order to expand knowledge and develop new tools. In addition, it is important that both parties remain continuously updated in the medical care processes of diseases such as multiple sclerosis, taking into account that symptomatic problems, despite improvements in their control, have a significant and negative impact on the patient's life. Therefore, it is important and necessary to have access to recent studies and information about the current and future prospects of the treatment of this pathology, which affect a considerable number of people of all ages and worldwide.

For the reasons stated above, this study aims to answer the following research question: what are the advances in therapeutic approaches for the treatment of multiple sclerosis?

Justification

This research is justified by the need to describe the advances in therapeutic approaches to clinically treat multiple sclerosis, as it is important to provide valuable, relevant and updated information on the respective management against this disease. Currently, there are very few studies carried out within this field and at the national level, the information found is scarce and outdated, therefore, the execution of this research is essential for the updating and contribution of knowledge.

From the theoretical point of view, the research is important because it contributes with updated therapeutic criteria for the respective treatment in patients diagnosed with multiple sclerosis. This will have a significant impact on the methods and procedures that are carried out for the control of the disease. From a methodological perspective, it can be said that the research methods used in the present study can be applied in future research and in other contexts.

In terms of practice, research offers high-value information to fill knowledge gaps within the health field. Therefore, this positively favors both medical professionals, teachers and students within the branch of health, as well as multidisciplinary teams specialized in the care of patients with multiple sclerosis, establishing a criterion when establishing a specific medication and administering it to the patient according to their need.

The results obtained will directly benefit patients diagnosed with multiple sclerosis, since much more current and appropriate criteria will be used to identify the type of medication or therapy needed to address the disease in a personalized and effective way.

CHAPTER 2 THEORETICAL FRAMEWORK

Conceptualization

Multiple sclerosis is an inflammatory, chronic and demyelinating disease of the central nervous system, considered autoimmune and with a complex interaction of genetic and environmental factors in its pathophysiology. Basically, it is a damage that manifests itself in the layers of the nerve fibers of the system, also called myelin, which is progressive, and depending on the location in which it is within the central nervous system, it can cause various symptoms. (11).

Almost half of patients with multiple sclerosis are affected by acute demyelinating optic neuritis at some point during the course of the disease. May be diagnosed clinically by a history of eye pain primarily associated with subacute intermittent blurred vision or even vision loss(11).

Its development is influenced by genetic and geographical-environmental factors. The disease can evolve in different ways, the most frequent includes outbreaks and periods of stability, although in many cases it develops progressively and continuously.(12).

Epidemiology of multiple sclerosis

Studies conducted in recent years show an increase in the prevalence of multiple sclerosis worldwide, determined mainly by an immune origin, where the immune system attacks its own tissues generating serious injuries. Experts have efficiently identified the prevalences thanks to the improvements of health systems within the technological scenario, since the development of multiple technologies have allowed to optimize medical methods, and in the case of MS, the use of magnetic resonances for a more effective diagnosis has been frequented(13).

Multiple sclerosis affects approximately 2.5 million people worldwide (14). The highest prevalences have been documented in countries that are generally characterized by high risk, such as: Scandinavia, United States, Southern Canada and the British Isles. Figures of 248 cases per 100,000 population have been reported in several regions of northern Scotland, and in Canada prevalences of 313 have been published in Saskatchewan in 2013.(15) and 261 in Ontario(16).

Countries such as Spain and Italy, considered as regions of classically medium prevalence are currently considered as medium and high risk areas, due to the upward trend of cases documented in studies. Meanwhile countries in the Middle East, such as Iran or Turkey and some Latin American countries have shown a significant change in the trend, moving from a low range to a medium range according to the prevalence results published by current studies (13).

In Ecuador, research on multiple sclerosis was conducted for the first time in 2008, it was established in that study that the city with the most cases was Quito with a total of 5.05 per 100,000 people. Another of the cities with the highest prevalence was Guayaquil with a total of 2.26 cases per 100,000 people; and also the city of Cuenca, finding a total of 0.75 cases per 100,000 people. These data show that there is a low prevalence of this disease in Ecuador. However, in 2016, a new study was done in Cuenca estimating a prevalence of multiple sclerosis of 3.88 per 100,000 inhabitants. (17).

In 2018, an epidemiological study was carried out taking patients from the Andean region as a sample, in which it was shown that the highest rate of cases diagnosed with MS was in the province of Pichincha (4.49/100,000 inhabitants) and Azuay (4.08/100,000 inhabitants). According to INEC in Ecuador, the provinces of Azuay and Pichincha, have a higher population density with respect to Caucasian and mestizo ethnic groups. (17).

Clinical forms of multiple sclerosis

Clinical forms are identified as follows (18):

1. Relapsing-remitting multiple sclerosis (RRMS), basically this is the classic form by which the disease appears, and is directly associated with 85% of patients who have been diagnosed at the beginning. This form generates very discreet lesions, but with progressive advances of days or weeks.
2. Primarily progressive multiple sclerosis (PFMS), this form is based on a progressive progression of the disease from the beginning, and can worsen rapidly. It does not present any type of outbreak and affects approximately 15% of diagnosed patients.
3. Secondarily progressive multiple sclerosis (SPMS), presents at the beginning in the form of outbreaks, however, subsequently transforms progressively, this form has some stabilization lapses and also causes mild or light remissions occasionally.
4. Recurrent progressive multiple sclerosis (PRMS), this form is characterized by progressive and incessant deterioration from the moment the disease begins. It evolves constantly and within its picture you can see quite clear remissions. This type of sclerosis appears in 5% of diagnosed patients.

Symptoms of multiple sclerosis

The symptoms of this disease presents a very varied spectrum of symptomatic manifestations, which can be transient or permanent and affect multiple systems of the human organism(19). The symptoms experienced by people with MS vary from person to person, however, the signs that appear frequently are: constant fatigue, vision deficit, intense pain, abnormalities in sensations, among others (20).
However, symptoms can be identified according to three categories. (21):

1. **Primary** symptoms: are those symptoms that appear as a result of acute demyelination of the CNS, this causes the patient to have fatigue, bladder deficit, paresthesias, among others.
2. **Secondary symptoms**: are those symptoms that derive from the primary alterations, in general, the sequelae are: urinary infections, spasticity, pain, among others (22).
3. **Tertiary symptoms**: are the symptoms that are presented by the psychological alterations of the patient, which are associated with work, family or affective issues (23).

Characterization of symptoms

The most common symptoms are (24):

1. **PAIN.** It has been defined as an unpleasant sensory and emotional experience that is associated with actual or potential tissue damage. It is one of the symptoms most identified by patients with the disease, with a prevalence between 23% and 90%, although it is difficult to determine it due to the subjective nature of this symptom. It occurs most often in women.

Pain can be classified by pathophysiological mechanisms as nociceptive pain or neuropathic pain. The first relates to the function of nociceptors found in bones, muscles, and tissues. Fundamentally, it acts as a protective mechanism against stimuli that cause or cause damage to tissues or organs (somatic or visceral). This type of pain in patients with multiple sclerosis is related to musculoskeletal changes and trauma or falls (joint pain due to ankylosing or disuse, myalgia, bladder spasms, dyskinesia, among others).

The neuropathic pain associated with multiple sclerosis is caused by damage to myelin (demyelination) and axons. This type of pain can be observed in patients with multiple sclerosis such as dysesthesia, trigeminal neuralgia, painful tonic spasms, Lhermitte's sign, among others.

2. **FATIGUE.** It is considered as a significant lack of energy both physical and mental, it occurs differently in people who present it, coinciding in the presence of exhaustion or fatigue that makes it difficult to perform activities of daily living. This is one of the most frequent symptoms in MS, occurring in approximately 75% of patients at some point during the disease.

3. **SPASTICITY.** It is considered as a disorder in motor ability that is usually manifested by an increase in tonic-stiral reflexes, that is, increased stiffness and involuntary muscle contractions due to upper motor neuron syndrome. It is a very basic symptom within the process that involves sclerosis, its prevalence shows that it has an existence in 60 – 75% of cases. Its manifestations are multiple, which can be asymptomatic, which can affect movement and cause pain. The treatment for this symptom is challenging because of the complex lesions that are generated within the central nervous system, among other secondary damages produced by the disease itself.

4. **HORMONAL SYMPTOMS.** This is one of the symptoms that most appears in patients, its prevalence is associated with 85% of cases. This symptom persists for a long time in the development of the disease and its beginnings are linked to damage to nerve tissues, which affect the bladder muscle and also injure the external urethral sphincter.

Risk factors

The risk factors that have been identified are(25):

✓ **Vitamin D deficiency.**

The action of vitamin D in stimulating lymphocytes and modulating growth and immune response indicates that it plays an important role in the pathogenesis of MS. In addition, there is an increase in innate immune system reactions and adaptive immune activity. Vitamin D reduces the production of Th1-mediated proinflammatory cytokines. Results in many trials indicated that vitamin D administration drastically altered levels of interleukin-10 (IL-10) and interleukin-17 (IL-17). Multiple sclerosis is more common in people who live further north or south of the equator. The prevalence rate in societies near the equator is almost zero, but increases to 50 cases per 1,000,000 people living 45 degrees north or south. Vitamin D insufficiency among patients may contribute to this regional distribution.

✓ **Genetics and family history**

There is evidence that some people have hereditary susceptibility to multiple sclerosis. Although, this genetic susceptibility is not inherited because there is no specific MS gene. Genetic studies have shown a connection between first-, second- and third-degree relatives.

✓ **Diseases**

It has been identified that bacterial or viral infections may promote the further development of this disease in genetically susceptible people. Disorders in late childhood can introduce foreign antigens that activate Th1 cells and induce the autoimmune response characteristic of multiple sclerosis(26).

✓ **Injury**

Severe injuries that directly damage the brain or spinal cord have been identified as possible triggers for multiple sclerosis. Trauma facilitates the entry of Th1 cells into the CNS. This is the initiating factor of the inflammatory response that leads to the destruction of myelin and the formation of potentially serious lesions.

✓ **Smoking**

Smoking increases the risk of developing multiple sclerosis. Smokers with the disease have a worse long-term prognosis and a higher incidence of brain atrophy than nonsmokers. In addition, MS patients are more likely to smoke than the general population. Patients with sclerosis are more likely than the global population to have comorbid conditions associated with poorer quality of life, higher burden of disability, and higher mortality rates.

Diagnosis

The diagnosis of multiple sclerosis is determined by evidence of the spread of the disease with features separated in space and time. Space diffusion refers to the presence of lesions in different anatomical locations of the CNS, including the infratentorial, juxtacortical, cortical, spinal cord, and periventricular area.

On the other hand, dissemination refers to the development of new lesions over time. MRI may demonstrate dissemination over time through the simultaneous presence of gadolinium enhancers (acute) and non-enhancing (chronic) lesions or development of a new T2 lesion on follow-up MRI. Diffusion over time can also be necessitated by multiple different clinical attacks (27).

Early and accurate diagnosis is critical and supported by diagnostic criteria from the incorporation of cerebrospinal fluid imaging and abnormalities for patients presenting with a clinically isolated syndrome. The diagnosis of MS is based on a combination of clinical findings, imaging and laboratory data using current diagnostic criteria known as the "McDonald Criteria".(27).

The criteria for the diagnosis of McDonald's multiple sclerosis are:

Criteria for the diagnosis of multiple sclerosis		
Clinical attacks.	**Magnetic resonance imaging (MRI) with clinical evidence objectives.**	**Additional data are needed for the diagnosis of multiple sclerosis.**
≥2	≥2	None [b]
≥2	1c	None
≥2	1	Diffusion into space (DIS) demonstrated by an additional clinical attack involving a different Central Nervous System (CNS) site or by magnetic resonance imaging (MRI).
1	≥2	Diffusion over time (DIT) demonstrated by additional clinical attack, magnetic resonance imaging or specific oligoclonal bands of Cerebrospinal Fluid (CSF).
1	1	DIS demonstrated by additional clinical attack involving a different area of the system or by MRI and DIT demonstrated by further clinical attack or by MRI, or demonstration of CSF-specific oligoclonal bands.
Primary progressive multiple sclerosis		
Required: 1 year of disability progression (determined retrospectively or prospectively) regardless of aggravation. Hypertensive lesions or those within the spinal cord should be considered, as well as those that have conditions within the functional system of the brain.		

Fountain: (28).

Treatment

The first modifying treatment (DMT) identified was an injectable drug approved by the Food and Drug Administration (FDA) in 1993. Following this, a variety of them have been developed: injectable, oral and infusion that have unique risks and benefits. (29). Research has shown markedly increased use of specific medications in cases of multiple sclerosis in the 5 years prior to the first demyelinating claim (30).

The therapeutic alternative for multiple sclerosis is widespread, both oral and by infusion for those who present the recurrent form of the disease. It is necessary to analyze the characteristics of the patient for the choice of the correct treatment, balancing the profile of side effects with the most clinically appropriate drugs or therapies. The choice of a more personalized medicine should be supported by clinical guidelines. A comprehensive management program is recommended for all patients with multiple sclerosis, in addition to improving quality of life through promoting well-being, addressing risk factors and managing comorbidities. (31).

The biggest remaining challenge is the steady advancement of treatments that incorporate neuroprotection and remyelination to treat and ultimately prevent progressive and disabling forms of the condition.

From a pharmacological perspective, there are four types of intervention. (32):

1. **Disease-modifying treatment**: This treatment actively seeks to decrease the outbreaks caused by the disease, as well as the reduction of deficiencies and other damage observed.
2. **Treatment of symptoms:** this treatment is intended to treat the signs that appear as a result of damage to the central nervous system, such as: bladder and cognitive deficit, spasms, movement deficiency, etc.
3. **Treatment of relapses or outbreaks**: this treatment proceeds with signs that are considered acute and are complex against the body's immune responses.
4. **Rehabilitation treatment**: this treatment is aimed at recovering the patient's motor functions and maintaining an optimal lifestyle.

In recent years, new therapeutic alternatives in multiple sclerosis have grown considerably. Disease modifiers include: (33):

a) Interferon beta 1 a. Route and frequency of administration: it is executed subcutaneously and a week they are applied 3 times.
b) Interferon beta 1 b. Route and frequency of administration: subcutaneous, half for one day.
c) Peginterferon beta 1 a. Route and frequency of administration: subcutaneous, every 2 weeks.
d) Glatiramer acetate. Route and frequency of administration: subcutaneously, once a day, a week 3 times.
e) Teriflunomide. Route and frequency of administration: ora, l once daily.
f) Dimethyl fumarate. Route and frequency of administration: oral, twice daily.
g) Fingolimod. Route and frequency of administration: oral, once daily.
h) Natalizumab. Route and frequency of administration: intravenous, once a month.
i) Alemtuzumab.Route and frequency of administration: intravenous, applied in two cycles, one year apart (34).
j) Ocrelizumab. Route and frequency of administration: intravenous, every 6 months).
k) Cladribine. Route and frequency of administration: oral, two cycles separated by one year.

Therapies or treatments of the disease may be discontinued in the following situations: (33):

1. If there is an erroneous diagnosis, it should be assessed if the treatment should really be applied in the patient due to its need, and should be discontinued if the reasons for which the therapy was indicated are not present.
2. The treatment should be discontinued if in the process a side effect arises as a result of the therapy itself, even more so when these effects tend to endanger the patient's life. In this sense, it should be clear that therapies that are new can generate certain complications in patients such as infectious agents, cardiac anomalies, hematomas, among others that can be lethal for the clinical condition, and therefore must be monitored progressively.
3. Treatment may also be interrupted by precautionary factors, i.e. when it is considered that there are factors that may increase the risk of certain adverse events and that, in addition, may endanger the patient's life. Each of the clinical components that will be used within the indicated treatment should be analyzed and compared with the condition in which the patient is, in order to find affinity between both. In this way, the risk of any dangerous situation is reduced.
4. Treatment may also be discontinued when there is evidence of non-compliance. That is, there is a lack of consistent adherence to therapy, therefore, when observing that there can be no control over it, it cannot continue.

CHAPTER 3 OBJECTIVES

Objectives

General objective:

To describe advances in therapeutic approaches to the treatment of multiple sclerosis: current and future perspectives.

Specific objectives:

1. Specify the most recent advances in pharmacological treatments used in the treatment of multiple sclerosis.
2. Identify the challenges and limitations associated with current therapeutic approaches in the management of multiple sclerosis.
3. Review future perspectives and emerging trends in the research and development of therapeutic approaches for multiple sclerosis.

CHAPTER 4 METHODOLOGICAL FRAMEWORK

Methodology

General design of the study

Narrative Literature Review

Selection criteria

Inclusion criteria

a) Articles published in the last 5 years.
b) Articles with complete information.
c) Articles in Spanish and English

Exclusion criteria

a) Articles from non-scientific or reliable sources.

Search strategy

Review of sources from different scientific databases, taking into consideration high impact articles present in NCBI, NESM, The Cell, Science, Springer Link, Elsevier, etc., published during the last five years, in Spanish and English, taking as keywords: multiple sclerosis, therapeutic approach, treatment, nervous system.

Data collection and extraction process

The information was organized according to the objectives defined for the review, according to an order based on the years of publication. If an article is valid for more than one objective, only the one that best fits the identified objective was considered. The articles available in PDF version will be compiled in digital folders to facilitate the use of the information in the bibliographic review. A Prism flowchart was used. The information was analyzed taking into account the organization carried out from the defined objectives.

CHAPTER 5

5. Results

Objective 1. Specify the most recent advances in pharmacological treatments used in the management of multiple sclerosis.

Author/ Year	Design	Objective	Sample	Results
Aguilar-Juarez, et.al (35). 2019	Review article	Give recommendations on different therapy approaches for multiple sclerosis.	n=1299 nephrology patients	Treatment received in adult patients: glatiramer acetate (18.2%), interferon beta 1b (17.4%), natalizumab (15.1%), fingolimod (14.8%), teriflunomide (12.5%), interferon beta 1 to 22 mg) 11.9%), interferon beta 1 to 30 mg (6 million) intramuscular (6.7%), interferon beta 1 to 44 mg (12 million (3.4%). 98% of adult patients diagnosed with MS had treatment. Treatment received by children and 100% of children received treatment: Inferon, 6, 8 and 12 million, glatimer acetate, teriflunomide, natalizumab, fingolimod, rituximab, azathioprine, mitoxanthrora, dimethyl fumarate. For the outbreak: methylprednisolone 1 g IV / is more than recommended and can be applied for up to 5 days depending on the intensity of the outbreak.
Juanatey A, et.al. (3) 2021	Retrospective cohort study	Characterize patients with MS	N=168 Women 70.8%	Type of MS: RRMS relapsing-remitting multiple sclerosis 72.6%, SPMS secondary progressive multiple sclerosis. 16.7% and PPMS primary progressive multiple sclerosis 10.7%. 78.8% received some disease-modifying drug, moderately effective drugs (interferon β, glatiramer acetate, teriflunomide or dimethyl fumarate) in 51.2%, and highly effective drugs (fingolimod, cladribine, natalizumab, ocrelizumab or alemtuzumab) 25.6%. Limitations are detected in the identification of MS incidence due to population aging and migratory flows.
Baskaran A, et.al. (5) 2023	Review article	Provide a detailed update on epidemiology, diagnosis, advances in treatment and important ongoing research in MS		Treatments: <u>High efficiency</u>: 1. Ocrelizumab (Ocrevus). Dosage: 300 mg IV × 2 doses 2 weeks apart, then 600 mg w/ 24 weeks 2. Ofatumumab (Kesimpta). 20 mg subcutaneously weekly at weeks 0, 1, 2, then 20 mg w/ 4 weeks from week 4 3. Natalizumab (Tysabri). 300 mg Intravenous V once a month. Option for c/ 6 weeks after 24 weeks of therapy. 4. Alemtuzumab (Lemtrada). Year 1:5 days of 12 mg Intravenous daily w/ steroids Year 2:3 days of 12 mg Intravenous daily w/ steroids <u>Medium to high efficiency</u> 1. Fingolimod (Gilenya). 0.5 mg orally daily.

				2. Siponimod (Mayzent). Start with 0.25 mg PO once daily on days 1 and 2; 0.5 mg on day 3; 0.75 mg day 4; 1.25 mg day 5 Maintenance: 2 mg once daily, starting day 6. 3.Ozanimod (Zeposia). Start: 0.23 mg once daily on days 1 to 4, and 0.46 mg on days 5–7, continuous 0.92 mg daily. 4. Cladribine (Mavenclad). 2 courses of oral treatment, each of 5 days and 1 year apart. Total dose of 3.5 mg/kg (1.75 mg/kg for each treatment. <u>Average efficiency</u> 1. Dimethyl fumarate (Tecfidera). Start: 120 mg Orally. After 7 days increase at the maintenance dose of 240 mg two v/d Take with food. <u>Low efficiency.</u> 1. INF β-1α (Avonex, Rebif, Plegridy) and INF beta-1b (Betaseron. Rebif 44 mcg subcutaneous TIW, Avonex 30 mcg, Plegridy 125 mcg intramuscularly once every 2 weeks. Betaseron 0.3 mg subcutaneous w/ two days. 2. Teriflunomide (Aubagio). 14 mg orally daily.

Objective 2. Identify the challenges and limitations associated with current therapeutic approaches in the management of multiple sclerosis.

Author/ Year	Design	Objective	Sample	Results
McGinley, M, et.al. (27) 2021	Systematic review	Summarize the current evidence on diagnosis and treatment of MS	108 items	**<u>Challenges:</u>** New therapies include cell-based therapies (hematopoietic and mesenchymal stem cells) and remyelination therapies with the potential to further improve MS treatment. -High-dose immunosuppressive therapy with autologous haematopoietic stem cell transplantation is not common, but there is evidence that it may have therapeutic effects. -An ongoing clinical trial (BEAT-MS [NCT04047628]) will evaluate the efficacy and safety of this treatment. Therapies that promote remyelination have the potential to delay or reverse disability. -Studies have been conducted with dissimilar compounds (e.g., biotin, clemastine and opicinumab, enchymal stem cells) evaluating the potential for remyelination **Limitations:** Data are insufficient and very limited.

Yang J, et.al. (10) 2022	Systematic review			**Limitations:** **1**. A shortage of effective treatments for progressive disease. New therapies are more effective at reducing relapse rates and MRI disease activity, but may have higher side effect profiles due to higher levels of immunosuppression. 2.Difficult disease management due to the diverse nature of the disease due to environmental and genetic factors, as well as the naturally adaptive and evolutionary nature of the immune system that changes with time and age. **Challenges:** 1**.** Develop neuroprotective and remyelinating therapies including mechanisms to support mitochondrial function and cell-based therapies targeting the causes of chronic inflammation. 2. Take advantage of additional therapeutic approaches immunoprotective mechanisms such as support of T-cell regulatory function and reparative microglial function. 3. Conduct further studies to identify risk factors for early increase in inflammatory state, early neurodegeneration, or a combination of both. 4. Perform therapeutic interventions early for the neuroinflammatory and neurodegenerative aspects of the disease for future therapeutic advances of the disease and true remission of it.
Gozzo L, et.al. (36)	Literature review	Provide a review of the current evidence on MS medication approved by the EMA in recent years.		**Treatments:** - Ponesimod. Adults with RMS with active disease observed by well-defined clinical elements. - Ofatumumab. Adults with RMS with active disease observed by clinical criteria or image support elements - Ozanimod hydrochloride. Adu Adults with RRMS with active disease as defined by clinic or Image features - Fumaric acid siponimod. Adults with PFMT with active disease evidenced by relapses or imaging features of inflammatory activity - Ocrelizumab. Adults with RMS with active disease defined by clinical or imaging features and adults with early PFMT and level of disability and with imaging features of inflammatory activity - Cladribine. Adults with highly active RMS as defined by clinic or Image features. - Peginterferon beta-1a. Adults with RRMS - Dimethyl fumarate. Adults with RRMS

				- Alemtuzumab. Adults with RRMS with active disease determined by well-defined clinical conditions. - Teriflunomide. Adults and pediatrics 10 years and older with RRMS - Fingolimod hydrochloride Adults and paediatric patients aged 10 years and older: with highly active disease.

Objective 3. Review future perspectives and emerging trends in the research and development of therapeutic approaches for multiple sclerosis.

Author/ Year	Design	Objective	Sample	Results
Bourque J, et.al. (11) 2021	Literature review	Present some experimental approaches that are currently being developed and are focused on modulating the functions of dendritic cells and regulatory T cells	-	**FDA-approved treatments:** 1. Interferon beta (currently available in three forms: IFN-b-1b, IFN-b-1a and pegylated IFN-b-1b) first-line option. Although not fully understood in the context of MS, IFN-b exerts broad anti-inflammatory and immunomodulatory effects. 2. Glatiramer acetate (GA), a mixture of synthetic polypeptides exerts a broad immunomodulatory action. 3. Dimethyl fumarate (DMF) and its bioequivalent diroximel fumarate, **Modifying therapies:** -Therapies that prevent lymphocyte migration thus preventing effector T cells from crossing the blood-brain barrier**:** fingolimod, siponimod, ozanimod and Ponesimod. -Natlizumab. Monoclonal antibody that binds to integrin a4. It prevents the transmigration of leukocytes, including activated autoreactive T cells, into the CNS. - Ocrelizumab. First choice for primary progressive MS. - Alemtuzu mab -Mitoxantrone. It acts as a topoisomerase type II inhibitor. -Cladribine. is a purine analogue that is incorporated into rapidly proliferating cells, including activated lymphocytes, and incorporated into DNA during synthesis, leading to DNA strand breakage and apoptosis. Teriflunomide inhibits de novo pyrimidine synthesis by blocking the enzyme dihydroorotate dehydrogenase, which also leads to apoptosis of proliferating T and B cells. **Future prospects**. -Phase III clinical trial. (NCT03896217) is currently investigating the use of simvastatin in secondary progressive MS (SPMS). Statins also exert anti-inflammatory effects and prevent the migration of leukocytes across the blood-brain barrier, making them a promising treatment for MS. -Phase III (NCT04291456) clinical trial investigating the use of minocycline that reduces the conversion of clinically isolated syndrome to multiple sclerosis. - Phase II trial. Ibudilast. Available orally for recurrent and progressive disease (MS) conditions. It works as an anti-inflammatory and reduces harmful immune responses.

				Two phase I trials (NCT02618902 and NCT02903537) investigate autologous myelin peptide-pulsed monocyte-derived dendritic cells (moDC) tolerated with 1a,25 dihydroxyvitamin D3 (tolDC-VitD3) in MS patients. Aim to induce tolerance of antigen-specific T cells that can modulate the course of the disease. - Phase II trial of the TCR peptide vaccine NeuroVax (NCT02057159).
Goldschmidt C, et al. (29) 2021	Revision		-	**Modifying therapies** **Injectable** Interferon b-1b was the first FDA-approved treatment. There are currently five interferon injections available for RRMS. Initial phase III trials with IFN-b found a reduction in relapse rates between 18% and 34% in patients with relapsing MS. -Glatiramer acetate with similar efficacy -Use of injectable therapies has decreased **Oral therapies** - Fingolimod the first approved (2010) - Siponimod and ozanimod. Similar to fingolimod, they have unique side effects and follow-up requirements. -Teriflunomide. Dose once daily. -Fumarate. Diroximel fumarate, with the same dosage and mechanism of action as dimethyl fumarate, but has better tolerability, specifically a reduction in gastrointestinal side effects. - Cladribine. Dose two cycles of 5 days 12 months apart. **Efficacy:** Oral injections are more effective than injectables, except teriflunomide, which has similar efficacy to injectables, and cladribine, which has the highest efficacy. Side effects: Increased risk of infections compared to injectables. **Infusions:** - Natalizumab. Monthly dose. High efficacy on relapses and magnetic resonance activity. Limited use due to risk of progressive multifocal leukoencephalopathy (PML). Not recommended for more than 2 years. - Rituximab. It has been used off-label in MS treatment, supported by evidence from phase II placebo-controlled trials demonstrating efficacy in RRMS. - Ocrelizumab, in treatment of RRMS and PFMS. S differs from rituximab by the potential to decrease infusion reactions. Used for its high efficacy, easy dosage and side effect profile. - Alemtuzumab. It is administered for 5 consecutive days in the first cycle, followed by a 3-day cycle one year later, with the possibility of retreatment. **TREATMENT STRATEGIES FOR RELAPSING REMITTING MULTIPLE SCLEROSIS**

				-Treatment should be tailored to each individual patient with respect to disease phenotype, risk profile and patient preference. -Climbing approach. Start with low to moderate efficacy, if breakthrough disease is present - Alternative approach. Initiate highly effective therapy as the first treatment option. -Treatments that are considered highly effective include **natalizumab, rituximab, ocrelizumab and alemtuzumab.** **Future perspectives**: 2 randomised multicentre trials in patients with treatment-naïve RRMS to rigorously evaluate the 2 treatment approaches: To determine the efficacy of early versus stepwise intensive approaches to treating the disease in its relapsing-remitting form (DELIVER-MS, NCT03535298) and trial of traditional therapy versus aggressive early therapy for multiple sclerosis (TREAT-MS, NCT03500328)
Reich S, et.al. (37)	Clinical trial	Determining a dose-response relationship between tolebrutinib and the reduction of new active brain lesions in relapsing MS	N=130	Treatment with tolebrutinib for 12 weeks. - Dose-dependent reduction occurred for new Gd-enhanced lesions (the 60 mg dose was the most effective) and was well tolerated by patients. -Efficacy in acute inflammation, combined with the potential to directly modulate the immune response within the CNS. Future prospects: Results provide scientific justification for phase III clinical trials in progressive and recurrent forms of MS
Schneider R, et.al. (38) 2022	Literature review	Identify peripheral and central mechanisms of action of BTKIs (Bruton's tyrosine kinase inhibitors and their recent use in MS)	-	**Future prospects:** BTKIs are a new type of molecules with potential to address unmet needs in MS clinical care, because they can exert beneficial effects on the adaptive and innate immune processes that underlie various aspects of the pathophysiology of MS. BTKIs may provide therapeutic benefits for people with MS without causing prolonged depletion of B cells and therefore may not carry the same risk of infection with chronic use. Available safety data for BTKIs are currently being evaluated in MS in a phase II trial of evobrutinib in MS (NCT02975349). In a phase II trial of tolebrutinib in MS (NCT03889639. Currently, none of the BTKIs tested have been validated by the FDA to treat Sclerosis M. Some of the BTKs analyzed may be approved by regulatory agencies for other indications in the near future. Ongoing phase III clinical trials of the various BTKIs will be essential to confirm the safety profiles of these agents

CHAPTER VI

6. Discussion

This literature review is aimed at describing advances in therapeutic approaches for the treatment of multiple sclerosis, as well as identifying current and future perspectives. The results obtained are limited by the insufficient documentation found on scientific evidence of the effectiveness of different therapeutic approaches in the management of multiple sclerosis, which continues to be a challenge for science.

The therapeutic alternative for the appendix of multiple sclerosis is wide, including those administered in injectable, oral and infusion forms which have both risks and benefits, hence choosing one of them implies taking into account the characteristics of the patient to balance the profile of side effects with the most clinically appropriate drugs or therapies. (31).

In recent years, new therapeutic alternatives have emerged in multiple sclerosis considerably, among the modifiers of the disease are interferon beta 1ª, as documented in a literature review by Aguilar et al.(35), in which it is noted that adult nephrology patients were administered Interferon beta 1 at 22 mg (11.9%), Interferon beta 1 at 30 mg (6 million) intramuscularly (6.7%), Interferon beta 1 at 44 mg (12 million (3.4%), 98% of adult patients diagnosed with MS had treatment.

Similar results were obtained by Juanatey et al. (3), in a retrospective cohort study in patients with multiple sclerosis of whom a smaller percentage received some disease-modifying drug and among them includes interferon, also reported by Baskarán et al. (5).

Other drugs used in the management of multiple sclerosis include acetate glatiramer, a drug belonging to the group of immunomodulators, documented by Juanatey A, et al. (3), Barboza A (33), Aguilar et al. (35), Mutlaq Y, et al. (39).

In the review by Dobson et al. (12)With the increasing number and efficacy of disease-modifying therapies, there has been increased interest in providing early treatment of MS to prevent long-term disability. Both immunosuppressive (fingolimod, natalizumab, ocrelizumab) and immunomodulatory (such as interferon beta, glatiramer acetate, teriflunomide) treatments have been used, indicating that ongoing treatment is required for suppression of inflammation and disease activity.

It is further proposed that immune reconstitution therapies (including alemtuzumab and cladribine) are possible to be used in short cycles in order to provoke certain immunological reactions with more durability, which involve the challenge of investigating whether early treatment prevents the disease. (12).

Similar to this result was evidenced in a review conducted by Aguilar-Juárez, et.al. (35) about the treatment given to adults with MS: with Natalizumab (15.1%), Fingolimod (14.8%), Teriflunomide (12.5%) and in children: natalizumab, fingolimod, rituximab, azathioprine, mitoxanthrora, dimethyl fumarate. It differs in the recommendation in the treatment of the outbreak that methylprednisolone should be administered depending on how severe the outbreak is. If there are quite severe outbreaks, plasmapheresis can be applied.

In a retrospective observational study in patients with multiple sclerosis, the most administered modifying therapy was dimethyl fumarate (19.1%), followed by teriflunomide (14.0%). Regarding parenteral modifying therapies, glatiramer acetate and natalizumab were the 2 most applied obtaining 11.1% and 10.8% (38).

It differs in the treatment given to patients with MS as documented by Juanatey et al. (3), where it is specified that 25.6% were administered cladribine, ocrelizumab or alemtuzumab) 25.6%, although in this study the identification of incidence of MS due to population aging and migratory flows is detected as a limitation.

The Challenges and limitations associated with current therapeutic approaches in the management of multiple sclerosis are evidenced as documented by McGinley et al. (27) in new cell-based therapies (hematopoietic, mesenchymal stem cells) and remyelination therapies with the potential to further improve the treatment of MS but the challenge of the therapeutic effects they can produce must be faced. The main limitation that arises is the insufficient and very scarce data that exist on this therapeutic procedure.

Other limitations have been documented by Yang et al. (10) Referring to the paucity of effective treatments for progressive multiple sclerosis and that newer therapies are more effective in reducing

relapse rates and disease activity by MRI but may have higher side effect profiles due to higher levels of immunosuppression.

A limitation noted in the studies refers to the management of the disease taking into account its diverse nature of both environmental and genetic factors, as well as the adaptive and evolutionary nature of the immune system that modifies with time and age. (10) unlike this, Ríos et al.(40), point out that there is still no clear and defined therapeutic scheme to follow in patients with MS that includes all the drugs approved and described in the literature.

In the Future perspectives and emerging trends in the research and development of therapeutic approaches for multiple sclerosis, Goldschmidt, C, et al.(29), point to the use of escalation approaches starting with low- to moderate-efficacy medications if breakthrough disease is present or an alternative approach initiating highly effective therapy as the first treatment option.

Two multicentre trials are proposed in the development perspectives to determine the efficacy of early versus stepwise intensive approaches to the treatment of relapsing-remitting disease (DELIVER-MS, NCT03535298) and trial of traditional therapy versus aggressive early therapy for multiple sclerosis (TREAT-MS, NCT03500328) (29).

Another proposal in the development of therapeutic approaches for the management of multiple sclerosis was proposed by Reich et al. (41), conducted in clinical trial to determine the dose-response relationship between tolebrutinib and the decrease of new active brain lesions in cases with relapsing MS, the results provided a scientific rationale for conducting phase III clinical trials in progressive and recurrent forms of MS.

Different clinical trials are being carried out taking into account that progressive forms of multiple sclerosis constitute an unmet need while therapeutic approaches have not been identified to respond to the progression of MS in the identified cases (36).

In the trends of research and development of therapeutic approach are those applied to the stage of development of adolescence. In this direction have been used as alternatives such as methotrexate, azathioprine, cyclophosphamide, rituximab, alemtuzumab and ocrelizumab, the efficacy and safety profile has not been specifically studied in children and adolescents by randomized methods and controlled clinical trials, which constitutes a limitation and challenge for science (36).

Future perspectives have been addressed in a literature review by Schneider et al. (38), to identify peripheral and central mechanisms of action of BTKIs (Bruton's tyrosine kinase inhibitors and their recent use in MS. The safety data available for BTKIs are currently being evaluated in MS in a phase II trial of evobrutinib in MS (NCT02975349) and in a phase II trial of tolebrutinib in MS (NCT03889639, at present, none of the BTKIs tested have been validated by the FDA to treat MS so conducting phase III clinical trials will be critical to evaluate safety profiles.

Conclusions

Scientific research has advanced in the development of new therapeutic approaches in the management of multiple sclerosis, a disease that even when there is no cure, modifying treatments can be administered that contribute to significantly reduce the risk of recurrence of the disease and delay the progression and development of disability.

Major disease-modifying therapeutic approaches include injectables (interferon, glatiramer acetate, ofatumumab); oral treatments such as teriflunomide, dimethyl fumarate, fingolimod, siponimod, cladribine, ozanimod, monomethyl fumarate, ponesimod), intravenous (ocrelizumab, talalizumab, alentuzumab) and new treatments such as Bruton's torokinase inhibitor (BTK), some of them have been approved by the Food and Drug Administration so it is necessary to continue developing studies that determine the efficacy and safety for better management of multiple sclerosis.

Among the future perspectives and emerging trends in the research and development of therapeutic approaches for the treatment of multiple sclerosis are, overcoming the current limitations of limited studies and clinical trials, in the therapeutic approach, in new and already approved drugs that allow to establish a therapeutic approach, precise for a better approach, thereby improving the quality of life of each patient.

The main **limitation** of this study lies in its design, which, being cross-sectional and applied in a short space of time, the studies and research included in it are insufficient.

Conflicts of interest.
The author does not declare conflicts of interest.

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ANNEXES

ANNEX no. 1 Flowchart