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Review

Exploring the Pathophysiology, Diagnosis, and Treatment Options of Multiple Sclerosis

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Abstract

The complicated neurological syndrome known as multiple sclerosis (MS) is typified by demyelination, inflammation, and neurodegeneration in the central nervous system (CNS). Managing this crippling illness requires an understanding of the complex interactions between neurophysiological systems, diagnostic techniques, and therapeutic methods. A complex series of processes, including immunological dysregulation, inflammation, and neurodegeneration, are involved in the pathogenesis of MS. Gene predisposition, autoreactive T cells, B cells, and cytokines are essential participants in the development of the disease. Demyelination interferes with the ability of the CNS to transmit signals, which can cause a variety of neurological symptoms, including impaired motor function, sensory deficiencies, and cognitive decline. Developing tailored therapeutics requires understanding the underlying processes guiding the course of the disease. Neuroimaging, laboratory testing, and clinical examination are all necessary for an accurate MS diagnosis. Evoked potentials and cerebrospinal fluid studies assist in verifying the diagnosis, but magnetic resonance imaging (MRI) is essential for identifying distinctive lesions in the CNS. Novel biomarkers have the potential to increase diagnostic precision and forecast prognosis. The goals of MS treatment options are to control symptoms, lower disease activity, and enhance quality of life. To stop relapses and reduce the course of the disease, disease-modifying treatments (DMTs) target several components of the immune response. DMTs that are now on the market include interferons, glatiramer acetate, monoclonal antibodies, and oral immunomodulators; each has a unique mode of action and safety profile. Symptomatic treatments improve patients' general well-being by addressing specific symptoms, including pain, sphincter disorders, fatigue, and spasticity. Novel treatment targets, neuroprotective tactics, and personalized medicine techniques will be the main focus of MS research in the future. Improving long-term outcomes for MS patients and optimizing disease treatment may be possible by utilizing immunology, genetics, and neuroimaging developments. This study concludes by highlighting the complexity of multiple MS, including its changing therapeutic landscape, diagnostic problems, and neurophysiological foundations. A thorough grasp of these elements is essential to improving our capacity to identify, manage, and eventually overcome this intricate neurological condition.

Keywords: multiple sclerosis; pathophysiology; clinical phenotypes; neuroimaging; treatment

1. Introduction

Multiple sclerosis (MS) is a neuroinflammatory disease of the central nervous system (CNS) that induces demyelination and neurodegeneration. It is one of the significant causes of disability in the young, affecting quality of life (QoL), family, work, and social activities [1].

The highest prevalence of MS is encountered in European Countries and the Americas, with 111–300 cases per 100,000 inhabitants [2]. In Asia, the prevalence decreases at 30 cases/100,000 inhabitants, while African Countries and West Pacific regions show the lowest prevalence (5 cases per 100,000) [2]. Environmental factors, lifestyle, and availability of medical resources may be responsible for the gradient observed in Countries with the highest socioeconomic status.

Regarding gender, MS mainly affects females with an overall ratio of 3:1. The mean age at diagnosis is estimated at 32 years. However, recent studies describe a shift towards older age at disease diagnosis [3,4]. Late-onset MS (LOMS) is defined as a diagnosis of MS at an age older than 50 years, and it now represents about 5% of cases. Several factors are responsible for this epidemiological change:

more extended life expectancy of the global population and the people with MS, improved disease diagnosis, treatment and care, and evolving diagnostic criteria [4]. LOMS and aging of people previously diagnosed with MS oblige to take into consideration comorbidities, age-related frailty, drug interactions, safety, and differential diagnosis of cognitive impairment.

Through the years, new insights in pathophysiology, improvements in diagnostic tools, and new therapies have changed the understanding of MS and the clinical management of people affected by this disease. The availability of several new therapeutic tools resulted in better disease control and improved QoL and disability; nevertheless, they also imply new and, sometimes, severe adverse events to be known, prevented, recognized, and treated.

The present review aims to provide an updated synthesis of the latest findings in the pathophysiology and clinical management of MS, emphasizing treatment options, especially disease-modifying therapies (DMTs).

2. Materials and Methods

The authors performed bibliographic research comprising English-language publications available on PubMed. Papers published within the last five years have been chosen preferentially, given the growing research activity in MS studies. However, previous relevant articles have also been selected. The search terms used are the following: "Multiple sclerosis" AND "pathogenesis" or "clinical course", "diagnostic criteria", "disease progression", "therapies", "disease-modifying therapies", "Bruton's tyrosine kinase inhibitors", "hematopoietic stem cell transplantation". Some articles were also derived from the bibliography of the chosen papers. Articles that were not in English and outside this review's scope and duplicates were excluded. A minimum of two of the authors reviewed each study for relevance.

3. Pathophysiology: From T Cells to Microglia

MS pathogenesis remains a complex and not yet well-known topic. MS develops in a complex interplay of genetic susceptibility and environmental factors.

Genome-wide association studies (GWAS) are still exploring the high complexity of polymorphisms in the genetic susceptibility of MS, which are commonly involved in intrinsic mechanisms of the immune system and autoreactivity. However, some human leukocyte antigens (HLA), such as HLA-DRB1*1501, are well-known risk factors, conferring a three times higher risk of disease [5].

Some environmental factors are strongly associated with the risk of developing MS. One of the most recently explored, the Epstein-Barr Virus (EBV) infection, has been shown to be correlated with a 32-fold risk of MS and to precede neuronal damage and neurofilament growth in cerebrospinal fluid (CSF) years before clinical symptoms [6,7].

Vitamin D levels and latitudinal gradient, cigarette smoking, childhood obesity, and low physical activity are other widely studied and modifiable risk factors for developing MS [8,9].

All these susceptibility factors lead to a decrease of regulatory and anti-inflammatory activity versus a more pro-inflammatory and auto-reactive immune system setting, with a reduction of T regulatory—Treg lymphocytes and an increased activity of pathogenic T helper (Th) 1 and Th17, which can cross the blood-brain barrier (BBB) and cross-react with oligodendrocyte antigens in the CNS [10].

Almost all immune cells have been postulated to participate in different moments of the disease duration. The wide range of mechanisms of action behind all the therapies approved for MS underline the disease's complex immunological pathway.

Historically, the "outside-in" hypothesis, in which a peripheral activation of autoreactive T cells, a decrease in regulatory T-cell activity, and a secondary migration toward the CNS, followed by inflammation and neurodegeneration of oligodendrocytes, had been for a long time considered the initial trigger of MS and, thus, T cells target therapies have been mainly investigated [11,12].

More recent findings have been supporting the possibility of a CNS trigger (inside-out hypothesis), probably derived from primary oligodendrocyte damage, as MS initial pathogenesis that, in a second time, activates autoreactive T and B cells in the CNS [11,12].

In this scenario, the contribution of B cell lineage has been primarily explored, and mechanisms underlying the efficacy of B-cell-depleting therapies have allowed a more exhaustive understanding of MS pathogenesis.

B cells in MS are believed to possess an abnormal ability to produce pro-inflammatory cytokines and, on the other hand, display less secretion of anti-inflammatory cytokines, such as interleukin 10 (IL-10). Moreover, adhesion molecules expressed on BBB cells facilitate the infiltration of activated B cells in the CNS [13].

B cells are also involved in presenting antigens to T cells and expressing antibodies-producing plasma cells, as noted in the CSF, with the widespread presence of oligoclonal bands in MS [14].

In pathological study of MS lesions, B cells are found to be expanded in MS lesions and participate in meningeal and perivascular inflammation. At the same time, they are almost absent in normal-appearing white matter [15]. The high efficacy of B cell-targeting therapies in MS strongly implies that B cells have a role in the pathogenesis of the disease.

However, some degree of CNS inflammation seems to persist despite the depletion of B cells (defined as "compartmentalized inflammation"). Some MS lesions display a persisting activation and chronic stimulation of T and B cells, even in the absence of clinical relapses, defined by the term "chronic active lesions", a hallmark of disease pro-

gression independent of relapse activity (PIRA). These lesions present a very small percentage of $CD20^+$ B cells and a higher proportion of mature B cells producing antibodies and infiltrating T cells [16].

Homeostasis of CNS resident cells and restoration of damaged oligodendrocytes and neurons are newly explored research fields. CNS resident mononuclear phagocytes (called "microglia") that, in normal conditions, preserve CNS homeostasis are activated toward a pro-inflammatory setting in active phases of MS disease and are the first to be found in MS lesions. Ongoing trials on new therapeutic approaches demonstrated reduced pro-inflammatory activity on activated microglia [17].

4. Clinical Features

MS clinical manifestations are heterogeneous, depending on the regions of the CNS involved. Moreover, signs and symptoms of the disease may present with both mono-focal and multifocal onset.

There are different ways to classify the clinical characteristics of MS according to the site and/or the mode of onset.

The following sub-points summarize the main clinical features, predominant lesional sites, and disease course.

4.1 Prodromes and Clinically Isolated Syndrome

Prodromes and early signs and symptoms of MS are often insidious; studies on clinical databases show that people affected by MS have a greater health-care use years before the official diagnosis for symptoms including pain, insomnia, fatigue, mood disorders, urinary and gastrointestinal non-specific symptoms [2,18]. Identifying the prodromal stage of MS is one of the future challenges in this field since prospective studies on this topic are still lacking.

Furthermore, some subjects present the characteristics of MS lesions on Magnetic Resonance Imaging (MRI) without any neurological signs or symptoms. This eventuality is defined as "radiologically isolated syndrome" (RIS) [19]. People with RIS show an increased prevalence of headache, cognitive impairment, and slower manual dexterity; furthermore, over five years, up to 50% of these subjects are diagnosed with a clearly defined MS [20]. Fast conversion to MS has been related to young age, spinal cord involvement, and enhancing lesions [21]. It is still unclear if any treatment may prevent the transition to MS; a trial with dimethyl fumarate effectively reduced the risk of a first clinical demyelinating event [22].

Clinically isolated syndrome (CIS) is represented by a single, often monophasic demyelinating event that does not fully satisfy the criteria for MS diagnosis. Up to 85% of people with MS presented a CIS as the clinical onset of MS [23].

The term CIS is applied to acute or subacute-onset episodes lasting at least 24 hours and reaching a peak rapidly within 2–3 weeks, in the absence of fever or infection and with no clinical features of encephalopathy. Signs and symptoms of CIS involve mainly the optic nerve (unilateral optic neuritis, blurred vision), brainstem and cerebellum (ataxia, cranial nerves involvement), and spinal cord (sensory and motor signs, urinary incontinence).

In most subjects, CIS will evolve to MS; however, a small portion will remain clinically stable. The number and localization of the lesions and the presence of oligoclonal bands (OCBs) in CSF are risk factors for evolution into MS [2]. Thanks to the 2017 revised McDonald criteria, earlier diagnosis of MS and, consequentially, a prompt start of disease-modifying therapies are possible [24].

4.2 Relapsing-Remitting MS

The most frequent MS phenotype is relapsing-remitting (RR), characterized by acute neurological impairment (relapses) alternated by periods of relative clinical stability (remissions).

Relapses are defined as the onset of new neurological symptoms and signs lasting at least 24 hours and unrelated to infections or metabolic imbalance.

The most frequent clinical features of MS are optic neuritis, brainstem and cerebellar syndromes, and myelitis, while supratentorial signs or symptoms are rare, especially at disease onset.

The optic nerve is often a site of demyelination; in fact, optic neuritis is frequently the clinical onset of MS. It typically consists of acute unilateral central acuity visual loss, with retro-orbital or peri-orbital pain that worsens with eye movement and impairment in color vision. The optic disc appears healthy or mildly swollen with no hemorrhage or retinal exudates [25].

Other sites usually attacked in MS are the brainstem, fourth ventricles, cerebral peduncles, cerebellar white matter, and cerebellar peduncles. Symptoms and signs range from diplopia to oscillopsia, internuclear ophthalmoparesis, gaze-evoked nystagmus, cranial nerve palsy, trigeminal neuralgia, limb incoordination, and ataxia [26].

MS often involves the medulla, causing acute myelitis, which presents with mild to severe asymmetric and/or symmetric sensory or motor symptoms, pyramidal signs, Lhermitte signs, sensory ataxia, and urinary and sexual dysfunctions [27].

The type and severity of the myelitis (transverse myelitis, caudal syndrome, posterior columns involvement, etc.) depend on the medullar site affected and the number of lesions.

Supratentorial signs and symptoms of MS are not frequent; they are represented by unilateral motor and/or sensory disturbances, homonymous visual field defects, seizures, and cognitive impairment.

Table 1. Brain and spinal cord Magnetic Resonance Imaging in the diagnosis of multiple sclerosis (MS).

- T2-weighted images: identify hyperintense lesions (plaques) in the white matter
- Fluid-attenuated inversion recovery (FLAIR) sequences: highlight lesions near the ventricles, corpus callosum, brainstem, and spinal cord
- Gadolinium-enhanced T1-weighted images: detect active inflammation indicated by enhancing lesions
- Lesions in typical sites

Different clinical features have recently been described to distinguish between early-onset MS (EOMS) and LOMS. EOMS is more likely to present visual and sensory impairment, while LOMS has more motor and urinary symptoms at onset, often associated with spasms, fatigue, and tremors [28]. Frequency of relapses, new T2-w lesions, or contrast-enhancing lesions at MRI represent measures of disease activity. The frequency of relapses tends to decrease in an age-dependent fashion, being higher in younger people [2].

Late diagnosis and, consequently, late treatment are associated with increased disability and progression to secondary progressive MS [29]. However, recent studies show that long-term disability is independent of relapse frequency, and it is associated with increased brain atrophy even at the early stages of the disease [30–32]. The presence of OCBs, high number of T2-w lesions (predominantly located in the spinal cord), older age, and brain atrophy are all related to increased risk of disability progression regardless of the frequency of relapses [30–32].

Luckily, thanks to DMTs and clinical management, a smaller proportion of people with RR MS evolve into secondary progressive disease [2].

Besides disability worsening, QoL may be compromised by reactive depression and cognitive impairment. The latter occur even in nearly all stages of the disease and are also described in the case of clinically and radiologically isolated syndromes [33]. In RR MS, cognitive impairment occurs in up to 40% of patients, reaching 70% in secondary progressive MS. The cognitive domains most often compromised are information processing speed, sustained attention, verbal fluency, conceptual reasoning, visual-spatial perception, episodic memory, and working memory. In patients with a more extended history of disease and subjects affected by LOMS, cognitive disability is frequent and more severe, also accounting for age-related comorbidities (cerebrovascular disease, for instance) and mood disorders [34]. For these reasons, cognitive assessment should be performed during neurological visits to identify patients who may benefit from specific treatments and cognitive rehabilitation [35].

4.3 Secondary Progressive MS

Secondary progressive MS is characterized by disability worsening without evidence of new acute inflammation both at neurological assessment and at MRI. Due to age-related functional decline and fluctuations of symptoms, secondary progressive MS is assessed retrospectively, some years after the chronic worsening [2]. There is also active secondary progressive MS when clinical relapses and new focal MRI lesions coexist with chronic worsening of disability.

Some studies attempt to detect the transition to secondary progressive MS early, based on clinical scores and the presence of contrast-enhancing lesions, spinal cord lesions, and cortical lesions at diagnosis [31,32,36].

Recent hypotheses suggest that RR MS and secondary progressive MS are not separate entities but a single continuum with common and overlapping pathophysiological mechanisms. Subjects' variability in phenotypical presentations and time to disability worsening may be explained by different neurological reserves and age-related frailty [37,38].

4.4 Primary Progressive MS

A small percentage of people present with primary progressive MS at diagnosis (10–15%), characterized by slow but constant disability progression despite treatments. It is still unclear whether primary progressive MS represents a particular phenotype distinct from secondary progressive MS or it just presents a long prodromal stage characterized by undiagnosed chronic inflammation and neurodegeneration [2].

5. Diagnostic Tools

The diagnosis of MS involves a comprehensive evaluation that includes clinical history, neurological assessment, imaging studies, cerebrospinal fluid analysis, neurophysiological exams (Evoked Potentials), and blood test.

The diagnostic work-up is guided by the 2017 revised McDonald criteria, which help Clinicians confirm the diagnosis based on objective evidence of demyelination disseminated in time and space [39].

Accurate and early diagnosis is crucial for effective management and improving the quality of life for individuals with MS.

5.1 Magnetic Resonance Imaging

Magnetic Resonance Imaging can support clinical information in diagnosing MS by showing disease dissemination in space (DIS) and time and by helping exclude MS mimics [2].

DIS describes the development of lesions in four distinct anatomical locations within the CNS: the periventricular brain region, cortical or juxtacortical brain regions, infratentorial brain region, or spinal cord. It can be shown by

Table 2. Quantitative Magnetic Resonance Imaging (qMRI) in MS.

qMRI technique	Key aspects of MS
T1 and T2 Relaxation Times	Information about tissue composition and myelin damage
Magnetization Transfer Ratio (MTR)	The integrity of myelin, with lower values suggesting demyelination
Diffusion Tensor Imaging (DTI)	Evaluation of microstructural changes in white matter, identifying areas of axonal injury and integrity
Quantitative magnetic susceptibility (QS) imaging mapping (QSM)	Measures of magnetic susceptibility and identification of iron accumulation and other pathological changes in tissues

one or more T2-hyperintense lesions characteristic of MS in at least two of the four areas mentioned earlier in the CNS (Table 1).

Dissemination in time (DIT) describes the development or appearance of new CNS lesions over time. It can be shown by the simultaneous presence of gadolinium-enhancing and non-enhancing lesions at any time or by a new T2-hyperintense or gadolinium-enhancing lesion on follow-up MRI compared to a baseline scan, irrespective of the timing of the baseline MRI (Table 1).

Conventional MRI plays an unquestionable role in diagnosing and managing MS [40,41]. However, it provides limited information regarding the pathophysiology of CNS damage because conventional sequences are not able to detect subtle changes affecting white and grey matter.

Moreover, conventional MRI does not allow a good correlation between the number of lesions and the severity of a disability, configuring the so-called "clinic-radiological paradox".

Multiparametric quantitative magnetic resonance imaging (qMRI) is an advanced imaging technique extremely promising for understanding the pathophysiology and monitoring the course of MS [42,43].

It typically includes various techniques to assess and differentiate tissue characteristics: T1 and T2 Relaxation Times, Magnetization Transfer Ratio (MTR), Diffusion Tensor Imaging (DTI), and Quantitative Susceptibility Mapping (QSM) [44]. Table 2 summarizes the main key aspects of each technique.

Multiparametric qMRI has several clinical applications in MS, such as:

○ early diagnosis and differentiation between MS subtypes.

○ monitoring disease progression.

○ evaluation of therapeutic responses.

○ biomarkers identification for predicting disease course and potential complications.

Furthermore, considering research fields, multiparametric qMRI allows a deeper understanding of MS pathophysiology and enables more tailored treatment approaches.

5.2 Cerebrospinal Fluid

The analysis of cerebrospinal fluid in suspected MS patients has regained attention in the latest version of the diagnostic criteria due to its diagnostic accuracy and increasing issues with misdiagnosis of MS based on over-interpretation of MRI. The hallmark of MS-specific changes in CSF is the detection of OCBs that occur in most MS patients (Table 3). Lack of OCBs has a very high negative predictive value, representing a red flag during the diagnostic work-up, and alternative diagnosis should be considered [39,45].

The 2017 criteria have been updated to include both symptomatic and asymptomatic brain and spinal cord MRI lesions to demonstrate DIS and time and cerebrospinal fluid-specific OBCs as a substitute for a second clinical event or MRI activity [39].

5.3 Evoked Potentials

Although MRI scans are more commonly used, evoked potentials still have a role, particularly at the earlier stages of MS. The most widely used test is visual evoked potentials, which measure the speed of electrical conduction from the eyes to the occipital cortex. Delayed responses suggest demyelination.

Somatosensory evoked potentials and brainstem auditory evoked potentials assess the integrity of sensory pathways, detecting subclinical lesions and providing potentially functional measures of therapies' benefits.

5.4 Blood Samples

Blood tests help rule out other conditions that can mimic MS, such as infections (Lyme disease, syphilis, HIV, etc.), vitamin deficiencies (B12), and autoimmune diseases (lupus, Sjogren's syndrome, etc.) [45].

5.5 McDonald Criteria

The McDonald criteria are a set of guidelines that incorporate clinical and laboratory evaluations, as well as MRI data, to establish MS diagnosis.

The first version of the criteria was published in 2001 by an international team led by Neurologist Ian McDonald. The criteria have since been extensively updated several times, most recently in 2017 revisions [39].

To fulfill a diagnosis of MS based on the 2017 McDonald criteria, an individual must have evidence of CNS damage that is disseminated in both time and space.

DIS includes MRI evidence of lesions in at least two of the following areas: periventricular, juxtacortical/cortical, infratentorial, and spinal cord.

Table 3. Cerebrospinal fluid analysis in the diagnosis of MS.

• Oligoclonal Bands: The presence of oligoclonal bands (OCBs) in cerebrospinal fluid (CSF) (not serum) indicates intrathecal immunoglobu--linG (IgG) production, seen in over 90% of MS patients
• Increased IgG Index: Elevated levels of IgG in the CSF relative to the serum

Table 4. The 2017 McDonald criteria for the diagnosis of Multiple Sclerosis.

• ≥2 clinical attacks
- with objective clinical evidence of two or more lesions
- with no additional data needed
• ≥2 clinical attacks
- with objective clinical evidence of one lesion and a clinical history of a previous lesion
- with no additional data needed
• ≥2 clinical attacks
- with objective clinical evidence of one lesion and no clinical history of a previous lesion
- with dissemination in space (DIS) evident on magnetic resonance imaging (MRI)
• 1 clinical attack (clinically isolated syndrome)
- with ≥2 lesions with objective clinical evidence
- with dissemination in time (DIT) evident on MRI or the presence of CSF-specific oligoclonal bands
• 1 clinical attack (clinically isolated syndrome)
- with 1 lesion with objective clinical evidence
- with DIS evident on MRI
- with DIT evident on MRI or the presence of CSF-specific oligoclonal bands

DIT, instead, includes MRI evidence and CSF-specific OCBs.

MRI Evidence of DIS is the simultaneous presence of both gadolinium-enhancing and non-enhancing lesions at any time or a new T2 or gadolinium-enhancing lesion on follow-up MRI, compared to a baseline scan, irrespective of the timing of the baseline MRI.

The diagnosis of MS can be made if there is fulfillment of any of the five categories of criteria reported in Table 4, depending on how many clinical attacks have occurred (Table 4).

6. Therapeutic Approach

Over the years, MS therapy has undergone several changes, both in terms of therapeutic targets and treatment paradigms [45–87].

6.1 Evolution in Therapeutic Targets

With regard to therapeutic targets, as previously mentioned, T cells and peripheral inflammation were broadly considered significant contributors to disease pathogenesis and demyelination in MS. Thus, first therapeutic approaches were based on the immunomodulatory properties of drugs against T-cells to decrease pro-inflammatory cytokines, increase T-regulatory function, and reduce the activity of matrix metalloproteinase [10] (Table 5, Ref. [60,61,73–87]).

Subsequently, further therapies were found to be effective in MS by reducing the lymphocyte trafficking across the BBB toward the CNS or by sequestrating peripheral lymphocytes to the secondary lymphoid organs, emphasizing the direct role of T-cell lineage in CNS damage (Table 5) [13]. Furthermore, it has been demonstrated that a more regulatory setting of immune systems follows depleting therapies, as observed with Alemtuzumab or hematopoietic stem cell transplantation [46,47]. After T and B cell depletion therapies, immune reconstitution follows a common pathway with $CD4^+$ cells raising faster and with a Th2 (anti-inflammatory/regulatory) phenotype, while Th1 and Th17 cells with a more pro-inflammatory setting reach normal values. This leads to a less inflammatory and less autoreactive setting of immune repertory and, accordingly, to a less aggressive MS phenotype [46,47].

The subsequent increasing role attributed to B cells in pathogenesis led to the development of new drugs directed precisely against certain B cells that have proven highly effective in controlling the disease.

Finally, future therapeutic developments will focus on restoring damaged oligodendrocytes, neurons, and pro-inflammatory-activated macroglia.

6.2 Evolution in Therapeutic Approach

The therapeutic paradigm is constantly evolving. In fact, it has been changed from the traditional “escalation therapy” approach, which involves starting treatment with medium efficacy treatment (MET), followed by a therapeutic shift to high efficacy treatment (HET), in case of uncontrolled disease, to early use of HET, often immediately at the diagnosis of MS [48–52].

Table 5. Disease-modifying treatments (DMTs) for MS and their mechanisms of action.

Therapy and market launch date	Route of administration	Mechanism of action	Side effects
Interferon Beta-1a (1997) [74]	Subcutaneous, intramuscular	Reduction of antigen presentation and T cell proliferation	Injection site reactions, "flu-like" syndrome, increased liver enzymes, depression, thyroid autoimmunity
Interferon Beta-1b (1993) [75]	Subcutaneous	Reduction of antigen presentation and T cell proliferation	Injection site reactions, "flu-like" syndrome, increased liver enzymes, depression, thyroid autoimmunity
Peg-interferon Beta-1a (2014) [76]	Subcutaneous, intramuscular	It has the same action as other interferons with the addition of pegylation	Injection site reactions, "flu-like" syndrome, increased liver enzymes, depression, thyroid autoimmunity
Glatiramer Acetate (1996) [77]	Subcutaneous	Shift from a pro-inflammatory T helper 1 (Th1) profile to a noninflammatory Th2 profile, with consecutively increased secretion of anti-inflammatory cytokines	Site reaction with possible risk of fat atrophy, increased liver enzymes
Dimethyl fumarate (DMF) (2013) [78]	Oral (twice/day)	Involves both nuclear factors erythroid-derived 2-related factor (Nrf2)-dependent and independent pathways, which lead to an anti-inflammatory, immune response due to type II myeloid cell and Th2 cell differentiation and neuroprotection	Increased liver enzymes, flushing, gastrointestinal effects, lymphopenia, rare Progressive multifocal leukoencephalopathy (PML)
Diroximel fumarate (2019) [79]	Oral (twice/day)	Similar to DMF, with less gastrointestinal adverse events	Increased liver enzymes, flushing, gastrointestinal effects, lymphopenia, rare PML
Teriflunomide (2012) [80]	Oral (once/die)	Selectively and reversibly inhibits dihydro-orotate dehydrogenase, a key mitochondrial enzyme in the de novo pyrimidine synthesis pathway, reducing the proliferation of activated T and B lymphocytes without causing cell death	Teratogenic effects, increased liver enzymes, hair loss, gastrointestinal symptoms, increased blood pressure, skin rash, peripheral neuropathy
Fingolimod (2010) [60]	Oral (once/day)	Modulates sphingosine-1 phosphate receptors with sphingosine-1-phosphate receptors (S1P) downregulation and Prevents exit of lymphocytes from lymph node tissue	Macular edema increases the risk of infection, bradyarrhythmia, risk of skin tumors
Ozanimod (2020) [81]	Oral (once/day)	Highly selective Sphingosine-1-Phosphate Receptor 1 (S1PR1) and S1PR5	Macular edema increases the risk of infection, bradyarrhythmia, risk of skin tumors
Ponesimod (2021) [82]	Oral (once/day)	Bind only S1PR1 receptor	Macular edema increases the risk of infection, bradyarrhythmia, risk of skin tumors

Table 5. Continued.

Therapy and market launch date	Route of administration	Mechanism of action	Side effects
Siponimod (2019) [73]	Oral (once/day)	Highly selective S1PR1 and S1PR5 modulator	Macular edema increases the risk of infection, bradyarrhythmia, risk of skin tumors
Cladribine (2019) [83]	Oral (five days on week 1, week 3, week 46, and week 48)	Selective, long-lasting depletion of B lymphocytes with a particular preference for memory B cells	Increased risk of infection, teratogenicity, potential increased risk of malignancy
Natalizumab (2004) [61]	Intravenous (every 28 days)	Anti-integrin alpha 4 (ITGA4) antibody: prevent adhesion to the endothelium of vessels, including those in the blood-brain barrier, by leukocytes expressing this integrin	PML, secondary antibody-mediated autoimmunity, increased liver enzyme
Ocrelizumab (2017) [84]	Intravenous (every sixth month)	Anti-CD 20 antibody depletes mature and immature circulating B cells	Infusion reaction, Lymphopenia, and increased risk of infection
Ofatumumab (2020) [85]	Subcutaneous (one/month)	Fully human Anti-CD 20 antibody depletes mature and immature circulating B cells	Site reaction, increased risk of infection, lymphopenia
Ublituximab (2022) [86]	Intravenous (every six months)	Anti-CD 20 antibody depletes mature and immature circulating B cells; potentially faster B cell depletion in clinical trials compared to other Anti-CD 20 approved drugs	Infusion reaction, Lymphopenia, and increased risk of infection
Alemtuzumab (2007) [87]	Intravenous (five infusions in year one and three infusions in year 2)	Depletion of CD 52 bearing T and B cell	Infusion reaction, Increased risk of infection, secondary autoimmunity, cardiovascular disease (aortic dissection, myocardial infarction, etc.)

Medium efficacy treatment (MET) are written in blue; high efficacy treatment (HET) are written in red. Launch date in brackets.

Table 6. Symptomatic therapy of MS (relating references in brackets).

Symptom	Therapy
Bladder dysfunction [99–102]	- Anticholinergic (oxybutynin) and antimuscarinic (darifenacin, tropism chloride) - Botulin toxin injection - Sacral neuromodulation with electrical stimulation of the S3 nerve roots as well as peripheral nerve stimulation of the dorsal penile or clitoral nerves and posterior tibial nerve
Fatigue [103–106]	- Ammantatine, modafinil, methylphenidate, carnitine supplementation
Pain [107–109]	- Antidepressants, antiepileptic drugs and opioids
Spasticity [110–113]	- Baclofen, tizanidine, benzodiazepines, cannabinoids, nabiximolo, botulin toxin, intrathecal baclofen, physical rehabilitation
Cognitive Symptoms [113,114]	- Cognitive rehabilitation, fampridine

This approach aims to reduce the risk of long-term disability accumulation. Increasing evidence shows that the risk of progression is only partly linked to clinical relapses and the presence of new inflammatory lesions on MRI. It is primarily connected with PIRA, which starts from the biological onset of MS [53–55].

An early start with HET is especially justified in the presence of one or more of the known risk factors for disease aggressiveness.

Increasing experience in the use of HET and more extensive availability of new drugs contributed to reducing the risk during treatment with HET [56].

In particular, several studies have proved that young patients (<40.5 years) seem to be optimal responders to HET and are burdened with fewer risks of severe adverse events [57–59].

A therapeutic issue that recently emerged is the management of MS onset in older adults, which is defined as LOMS (>50 years). The complexity of such therapeutic management is represented by the close link between age, comorbidity, physiopathological mechanisms, and immunosenescence among this population.

Indeed, all data from the main randomized controlled trials (RCTs) refer to patients <55 years, <50 years, or even <45 years [60–63], which makes the decisions on the efficacy and the safety of these drugs in LOMS even more difficult. Several studies have tried to analyze the effect of different treatments on disease progression and activity [64–68]. They showed that efficacy decreases in older patients, with a higher risk of adverse events.

Furthermore, an older age leads to a spontaneous increase in infections, neoplasia, and lymphopenia. These risks seem to increase due to a synergistic effect caused by DMTs use (e.g., higher risk of cryptococcal meningitis in patients receiving SP-1 modulator, higher infective risk in patients receiving anti-CD 20, higher herpetic infection, etc.) [69,70].

In addition, the risk of higher drug interaction in patients receiving polytherapy must be taken into account, also due to increased predominance of diabetes, stroke, ischemic heart disease, and congestive heart failure in people with MS [71].

Considering older patients with MS, menopause is worthy of consideration: around 30% of the MS population includes women in peri- and menopause. Schweitzer *et al.* [71] suggested a decrease in relapse rate and an increased disability progression post-menopause, data that further studies have not confirmed. In general, it seems that hormonal fluctuations coupled with immunosenescence contribute to neuroinflammation and neurodegeneration, increasing MS-related disability post-menopause [71].

6.3 Actuality and Future of Therapy in MS

The drugs used to treat the RR phenotype have been divided into medium-efficacy and high-efficacy treatments (Table 5) [56].

Ocrelizumab is the only drug approved for treating the primary progressive form of the disease [72].

Siponimod, instead, has been approved for secondary progressive MS [73], while several other drugs have been considered for the relapsing-remitting form, as listed in Table 5 (Ref. [60,61,73–87]).

The choice of a drug must be based on different elements: clinical and neuroradiological disease activity, patients' age, preference, comorbidity, and lifestyle.

An additional therapeutic option is autologous hematopoietic stem-cell transplantation [88].

This treatment allows long-term immunomodulation without the need for continuous use of DMTs. This procedure has a high number of risks and is, therefore, currently reserved for patients with a very aggressive form of disease that does not respond to other therapies. It is, however, a procedure in continuous development, with ongoing trials even on primary and secondary progressive forms of the disease.

As already described, research is focused on optimizing therapeutic options for already known pathogenic mechanisms and developing drugs for new targets (e.g., microglia activity, etc.).

A new class of DMT is currently being studied, named Bruton's tyrosine kinase inhibitors (IBtK). Bruton's tyrosine kinase (BTK) is a non-receptor, cytoplasmic tyrosine kinase expressed, very important for the development of B-cells and myeloid cells, located both peripherally and within the CNS [89–91].

In the pathogenesis of multiple sclerosis, BTKs lead to the release of pro-inflammatory cytokines, including interferon-gamma and tumor necrosis factor (TNF) alpha; such cytochemical release can lead to differentiation of $TCD4^{+}$ cells implicated in demyelination and activation in a pro-inflammatory sense of the macrophage component. BTKs are also present in microglia with activation of microglia themselves. The use of BTKs may mediate all these mechanisms, becoming a possible interesting new therapeutic approach to multiple sclerosis.

Studies are also underway to evaluate new targets for treating MS, hypothesizing possible mechanisms of remyelination or neuroprotection. In particular, trials focus on clemastine, alone or in combination with metformin [92,93].

Furthermore, interesting data come about exosomes, which can be secreted by neurons and glial cells and appear to be able to play an essential role in the autoimmune processes. Exosomal microRNAs (miRNAs) differ in their expression patterns in MS; these microvesicles are non-immunogenic and non-toxic therapeutic tools for transferring miRNAs across the BBB [94].

Another possible future target, with anti-inflammatory, neuroprotective, and remyelinating activities, could be ApTOLL. It is an aptamer selected to antagonize toll-like receptor 4 (TLR4), an essential actor of innate immunity involved in inflammatory responses in MS and other diseases [95].

Finally, other future therapeutic targets under investigation are related to the likely pathogenetic role of the EBV (allogenic Epstein-Barr virus T cell approach), preventive vaccine strategies, and the possible role of the gut microbiome [96–98].

6.4 Ancillary Therapies

Apart from DMTs, other treatments represent a standard of care in MS patients. People with MS are affected by several symptoms, such as pain, spasticity, and fatigue, that significantly impair everyday life activity and worsen the QoL.

Symptomatic therapies are, thus, mandatory to improve the overall well-being of patients with MS [99].

A list of these ancillary therapies is reported in Table 6 (Ref. [99–114]).

7. Conclusions

MS is a continuously evolving pathology both *per se* and according to epidemiological, pathogenetic, and therapeutic points of view. There are still many unmet needs for people affected by MS, and future challenges are represented by the treatment of LOMS, whose prevalence is likely to increase in the following years, the choice among many highly effective therapies since MS onset, the management of side effects, and the evaluation of possible strategies of de-escalation. Finally, new therapeutic targets aimed at controlling not only inflammatory activity but also neurodegeneration are needed to prevent the most insidious and "dark" side of MS.

Abbreviations

BBB, blood-brain barrier; BTK, Bruton's tyrosine kinase; CIS, clinically isolated syndrome; CNS, central nervous system; CSF, cerebrospinal fluid; DIS, dissemination in space; DIT, dissemination in time; DMF, dimethyl fumarate; DMTs, disease-modifying treatments; DTI, diffusion tensor imaging; EBV, Epstein-Barr virus; EOMS, early onset multiple sclerosis; FLAIR, fluid-attenuated inversion recovery; GWAS, genome-wide association studies; HET, high efficacy treatment; HLA, human leukocyte antigen; IBtK, Bruton's tyrosine kinase inhibitors; LOMS, late-onset multiple sclerosis; MET, medium efficacy therapy; miRNAs, microRNAs; MRI, magnetic resonance imaging; MS, multiple sclerosis; MTR, magnetization Transfer Ratio; OCBs, oligoclonal bands; PIRA, progression independent of relapse activity; qMRI, quantitative magnetic resonance imaging; QoL, quality of life; QSM, quantitative Susceptibility Mapping; RCTs, randomized controlled trials; RIS, radiological isolated syndrome; RR, relapsing-remitting; TNF, tumor necrosis factor; TLR, toll-like receptor.

Author Contributions

GP, SL, IDN, and LV did the PubMed research search for this review paper, wrote the paper, prepared the tables, and provided the final approval of the version of the article; LS, CS, MM, and CG assisted in the research, helped prepare the methods section, assisted in the tables, edited the paper, and provided the final approval of the version of the article; MZ assisted in the conception and design of the study, writing, outline, final approval of the version of the article to be published and completed the English and scientific editing. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

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Conflict of Interest

The authors declare no conflict of interest.

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