Acta Neurophysiologica
ISSN: 2996-7554

Academic Strive
Researcher's perception is our reality

Review Article *Volume 5 Issue 3*

Recent Advances in Multiple Sclerosis

Surya N[1]*, Someshwar H[2] and Ramamurthy G[3]

[1]Bombay Hospital and Medical Research Center, India
[2]Topiwala National Medical College and BYL Nair Ch. Hospital, India
[3]BG Institute of Neurosciences and Neurorehab, BG Hospital, India

***Corresponding author:** Nirmal Surya, Consultant Neurologist, Bombay Hospital and Medical Research Center, 310, Lotus House, New Marine Lines, Mumbai-400020, Maharashtra, India, Email: nirmal_surya@yahoo.com

Received Date: June 21, 2024; **Published Date:** July 24, 2024

Abstract

Multiple Sclerosis (MS), an enduring autoimmune condition impacting the central nervous system, presents a multifaceted landscape for exploration and treatment. Encouraging progress in diverse realms over recent years in stills optimism for enhanced care and potential breakthroughs. Diversification of treatment avenues: Novel medications such as cladribine and ocrelizumab are broadening the arsenal against MS, with ocrelizumab notably securing approval for all four MS types. Addressing neurodegeneration: Initiatives targeting nerve damage repair, including remyelination and neuroprotection, are gaining traction in research, holding promise for influencing progressive forms of MS. Precision medicine: The exploration of individual disease profiles and customized treatment strategies offers potential for tailored therapeutic approaches. Diagnosis and prognosis refinement: Development of new biomarkers, extending beyond MRI, is underway to facilitate more precise diagnosis, predict disease progression, and monitor treatment responses. Timely intervention: Recognition of early indicators through advanced methods such as blood tests could pave the way for prompt intervention and potential disease modification. Challenges and Prospective Trajectories: Progressive forms: The quest for effective treatments for progressive MS poses a formidable challenge, necessitating dedicated research endeavors. Personalized medicine: Integration of precision medicine into clinical practice encounters practical and ethical obstacles that must be surmounted. MS Cure: While a comprehensive cure remains elusive, integrated strategies addressing various facets of the disease harbor the potential to significantly enhance the quality of life for patients. In summary, recent advancements in MS research paint an optimistic picture. The expansion of treatment options targeted therapeutic approaches, refined diagnosis, and the pursuit of personalized medicine collectively shape the future landscape of MS management. Despite persistent challenges, ongoing research holds the promise of further elevating the well-being of individuals grappling with this intricate condition.

Keywords: Multiple Sclerosis; Medical Management; Recent; Rehabilitation; Diagnosis

Abbreviations

MS: Multiple Sclerosis; CNS: Central Nervous System; PET: Positron Tomography; TSPO: Translocation Protein; NAA: N-Acetyl Aspartate; TSC: Total Sodium Concentration; DWI: Diffusion-Weighted Imaging; DTI: Diffusion Tensor Imaging; NODDI: Neurite-Focused Diffusion and Density Imaging; CSF: Cerebrospinal Fluid; OCB: Oligoclonal Bands; FLC: Free Light Chains; CIS: Clinically Isolated Syndrome; DMT: Disease-Modifying Drugs; Btki: Bruton Tyrosine Kinase Inhibitors;

RRMS: Relapsing-Remitting Multiple Sclerosis; AHHSCT: Autologous Hematopoietic Stem Cell Transplantation.

Introduction

Multiple sclerosis (MS) is the leading cause of disability in young adults, and its causes have been well studied for more than a century [1]. Despite significant progress in understanding the immunity, genetics, and epidemiology of multiple sclerosis, its underlying mechanisms remain unclear. MS is characterized by changes characterized by relapsing-remitting attacks, in which patients often experience mental and radiological deterioration followed by different relapses or (remitting MS or RRMS) [1]. In most cases, these early stages are followed by more severe stages (progressive MS or SPMS), while a minority (about 15%) progress from initial (e.g., progressive MS) or PPMS for some reason1. Traditionally, the cause of multiple sclerosis has been explained by the "outside-in" autoimmune hypothesis, which proposes that dysregulated autoreactive T cells enter the central nervous system (CNS) from the periphery and interact with macrophages and B cells [1]. The cells target various parts of the central nervous system, especially myelin. This inflammatory process occurs in a recurrent clinical course and results in the accumulation of damage to the central nervous system. Therefore, many studies have focused on the autoimmune inflammatory nature of the disease, leading to many clinical recommendations. But another "inside-out" theory challenges this model, arguing that the initial failure occurs in the central nervous system1. Similar to other neurodegenerative diseases such as Alzheimer's and Parkinson's, this theory suggests that multiple sclerosis is primarily a degenerative disease with varying degrees of inflammation. This results in the release of cellular antibodies such as myelin oligodendrocyte glycoprotein, myelin simple protein, and proteolipid protein. Prolonged removal of these autoantigens then leads to an autoimmune inflammatory response, perpetuating further degeneration in a vicious cycle. The range of MS phenotypes is determined by the degree of inflammatory activity, which varies between patients as well [1]. More importantly, the "inside-out" perspective suggests that significant changes are present from the outset, perhaps years before symptoms first appear, and yet are found throughout the organism. Although today's treatments are effective in controlling the central nervous system in multiple sclerosis, the current challenge lies in addressing step by step the stage at which most of the disruptions occur. Understanding the mechanisms that drive these stages and improving the quality of treatment of patients with severe damage in the absence of disease remains an important goal in multiple sclerosis research [1]. The aim of this review is to highlight recent findings and discuss the pathogenesis of multiple sclerosis.

MS Pathophysiology

Although inflammatory-mediated demyelination of some of the axonally spared white matter tracts is a feature of multiple sclerosis (MS), recent advances in histopathology and imaging techniques have highlighted significant cortical demyelination [2]. Cortical demyelination, particularly in the cerebellar cortex, hippocampus, and deep gray matter nuclei, is an important histological aspect of multiple sclerosis. There is ample evidence that gray matter involvement is associated with disease activity and more types of MS [2]. Recent studies have shown that cortical and deep gray matter in the early stages of the disease are not associated with white matter pathology; This supports the idea that has been proposed for decades that neurodegeneration in multiple sclerosis is not related to inflammation. This is consistent with the concept of "silent progression," which suggests that the degenerative process is often independent of autoimmune inflammation. Compared to relapsing MS, inflammatory relapses are associated with short-term disability and long-term disability [2]. Progression of multiple sclerosis does not appear to be associated with recovery. Age and gender differences between relapse of MS and initial progression of MS do not necessarily mean differences in etiologies; they can be attributed to the hallmark of autoimmune disease. Peripheral immune cell infiltration in active demyelinating plaques is more prominent in relapsing MS, whereas progressive MS can lead to different pathological processes in resident CNS cells. Microglia, the most resident macrophage-like cells in the central nervous system, play an important role in preventing neurotoxic diseases or supporting neuroprotection, reducing pain and promoting healing [2]. Activated microglia located in areas adjacent to early active lesions and plaques may cause continued degeneration or play a protective role. Positron tomography (PET) imaging studies using a radioligand that binds to the 18-kDa translocation protein (TSPO) of activated microglia show increased TSPO binding in normal white matter of patients with multiple sclerosis. TSPO-PET studies have shown that the increase in gray subcortical areas, especially the thalamus, is associated with brain atrophy in secondary multiple sclerosis. However, the precise function of microglia to a constant extent in progressive MS is unclear [2].

New Imaging Technique

Over the years, proton magnetic resonance imaging (1H-MRS) has been used to investigate in vivo mitochondrial dysfunction in multiple sclerosis (MS) [3]. The MAGNIMS (MS Magnetic Imaging) European Network provides specific guidelines for its use. N-acetyl aspartate (NAA) concentration in 1H-MRS has become an important indicator for assessing the energy metabolism of the central nervous system (CNS) neurons. It tends to decrease after serious injuries but is partially

reversible. Additionally, 1H-MRS has been used to evaluate the role of other metabolites in MS-related neurodegeneration. High glutamate concentrations (indicative of glutamate toxicity) are associated with decreased brain function and disability, whereas decreased levels of gamma-aminobutyric acid (possibly upregulating axonal firing) are associated with reduced motor function in patients with multiple sclerosis [3]. A new metabolic imaging technique has emerged to measure mitochondrial dysfunction by assessing the increase in intracellular sodium, a key step in the cascade that leads to energy failure in neuronal cells. Sodium imaging estimates total sodium concentration (TSC) in the brain of multiple sclerosis patients, thereby indirectly measuring the axonal dysfunction that precedes neurodegeneration3. Recent advances, including new techniques for ultra-high-field MRI (7T), allow direct measurement of intracellular sodium concentration. In a study comparing patients with MS and healthy controls, patients with MS showed increased intracellular sodium concentrations in normal white and gray matter, accompanied by a decrease in the intracellular sodium volume ratio; this suggests that axonal dysfunction and cellular potential expansion in extraspace occur simultaneously on the inner face. In the metabolic pathogenesis of multiple sclerosis. Diffusion-weighted imaging (DWI) plays an important role in demonstrating the movement of microscopic water molecules in biological tissues. Although diffusion tensor imaging (DTI) has become the standard for studying central nervous system (CNS) pathology, its oversimplified model lacks the sensitivity and specificity to detect structural changes in MS. To address these limitations, new DWI methods such as neurite-focused diffusion and density imaging (NODDI) have been developed. Launched in 2012, NODDI can estimate specific parameters such as neurite density, orientation, and cerebrospinal fluid-like composition; This suggests that MS is more sensitive than DTI measurements and specifically for neurodegeneration [3].

Diagnosis

The diagnosis of multiple sclerosis (MS) involves a comprehensive evaluation, combining clinical signs, symptoms, magnetic resonance imaging, and cerebrospinal fluid (CSF) analysis [4]. Evidence of intrathecal immunoglobulin G (IgG) synthesis in the CSF, though not MS-specific, enhances diagnostic certainty. The gold standard for confirming this synthesis is the identification of CSF-restricted oligoclonal bands (OCBs) [4]. B cells, responsible for producing immunoglobulins, also release excess light chains as free forms. In chronic inflammatory CNS diseases like MS, free light chains (FLCs) accumulate in the CSF. Technological advancements in the early 21st century allowed for the quantitative detection of FLCs, facilitated by the development of detection antibodies targeting unique FLC epitopes. Evidence supporting the diagnostic accuracy of intrathecal κ-FLC synthesis in differentiating patients with multiple sclerosis (MS) and clinically isolated syndrome (CIS) from those with other neurological illnesses has been synthesized through a thorough systematic review and meta-analysis [4]. κ-FLC›s performance was contrasted with that of oligoclonal bands (OCB). The κ-FLC index was the focus of the analysis, which was based on 32 studies with about 3300 CIS/MS patients and 5800 control people [4].

The diagnostic sensitivity of the κ-FLC index ranged from 52% to 100% (weighted average: 88%) whereas the specificity showed a range of 69% to 100% (89%). By contrast, OCB showed a specificity of 74% to 100% (92%), and a sensitivity of 37% to 100% (85%). Using a bivariate mixed model that preserves a statistical power of while accounting for both within- and between-study variability the analysis indicated that the diagnostic accuracy of the κ-FLC index and OCB are comparable [4].

Therapeutic Advances

In the era of Interferon and Anti-Trafficker drugs such as Natalizumab and Fingolimod, the landscape of Multiple Sclerosis (MS) management witnessed significant strides. These medications played a pivotal role in controlling the disease, offering relief to patients. However, the paradigm of MS management underwent a transformative shift with the introduction of B Cell Depletors. This new class of drugs, exemplified by agents like Ocrelizumab and Rituximab, marked a substantial departure from traditional approaches. By specifically targeting B cells, these therapies aimed at modulating the immune response in a more precise manner. As we navigate this evolving terrain of MS management, it becomes crucial to explore the latest entrants in the field. The discussion will delve into the mechanisms, efficacy, and potential benefits of these emerging treatments, providing a comprehensive understanding of the evolving strategies in the management of Multiple Sclerosis.

Cladribine

Approved by the FDA in 2019, Cladribine is an oral medication used to treat relapsing forms of MS, excluding treatment isolation (CIS) [5]. As a prodrug, cladribine undergoes phosphorylation to produce the active metabolite cladribine 2-chlorodeoxyadenosine triphosphate. This reactive metabolite accumulates in the brain and affects cellular metabolism, DNA synthesis, and repair. Remember, cladribine is unique among oral disease-modifying drugs (DMTs) in that it is not taken every day (5.1). The use of body weight (3.5 mg/kg) involves a two-year cycle of two cycles each, 1 month apart. Cladribine is selective for lymphocytes by affecting CD4 + and CD8 + T cells and CD19 + B cells,

which phosphorylate cladribine due to its high concentration of deoxycytidine kinase. The CLARITY study, a randomized, double-blind, placebo-controlled trial, showed annual reductions compared to placebo, with reductions of 54-57% in both drug groups. The odds ratio of noncompliance was 2.53 (95% CI 1.87-3.43) for the 3.5 mg/kg dose and 2.43 (95% CI 1.81-3.27) for the 5.25 mg/kg dose was. However, caution should be exercised when selecting patients to receive cladribine because it is associated with the risk of malignancies, including benign uterine fibroids, melanoma, pancreatic cancer, and ovaries. A meta-analysis comparing cancer rates in studies of cladribine with other DMTs found no significant difference. Safety monitoring has shown that approximately 86% of patients develop lymphopenia approximately 2-3 months after starting treatment [5].

Bruton Tyrosine Kinase Inhibitors (BTKi)

Bruton Tyrosine Kinase Inhibitors (BTKi) represent an oral treatment for multiple sclerosis (MS) (5.2). BTK belongs to the Tec family of tyrosine kinases and is expressed in B cells, monocytes, neutrophils, and mast cells and plays an important role in B cell maturation, proliferation, antigen presentation, and plasma brain differentiation. In myeloid cells such as monocytes and granulocytes, BTK is important for the production and phagocytosis of cytokines and inflammatory mediators. Importantly, BTK is also expressed in microglia and is associated with neuroinflammation in progressive and relapsing MS phenotypes, making it an attractive target for the treatment of both types of MS [6]. Evobrutinib is a highly selective and irreversible oral BTKi and has been shown to be effective by reducing T1 gadolinium-enhancing lesions in phase 2 studies. Although there was no significant difference in annual recurrence between placebo and low- and high-dose evobrutinib. Tolebrutinib (another CNS-penetrating BTKi) demonstrated dose reduction in T1 gadolinium-enhancing lesions in a 12-week phase 2b randomized, double-blind, placebo-controlled crossover study [6]. Orelabrutinib is also a CNS-targeted BTKi currently in Phase 2 clinical trials for the treatment of relapsing-remitting multiple sclerosis. Many on-going phase 3 clinical trials aim to actively further investigate the effectiveness of BTK inhibitors (clinicaltrials.gov: NCT04410991, NCT04410978, NCT04458051) [6].

Ofatumumab

Ofatumumab is a monthly subcutaneous injection that was approved in 2020 (5.3). This monoclonal antibody targets CD20+ B cells, causing B cell depletion. Note that ofatumumab is different from other CD20 treatments; because it has a short half-life and is initially absorbed by lymph nodes after subcutaneous administration. Two important clinical studies demonstrate the effectiveness of ofatumumab in the treatment of relapsing-remitting multiple sclerosis (RRMS) (5.3). The Phase 2b MIRROR study demonstrated an average 65% reduction in the incidence of new gadolinium-enhanced MRI lesions compared to placebo after 12 weeks (incidence relative value 0.36, $p < 0.001$) (5.3). Post hoc analysis also showed a decrease in the corresponding values (0.07 to 0.25 compared to placebo, ratio 0.08–0.29, $p \leq 0.02$). ASCLEPIOS I and II studies, phase 3 double-blind, double-dummy, randomized controlled trial comparing ofatumumab and teriflunomide. The annual relapse rate in trial 1 was 0.11 in the ofatumumab group and 0.22 in the teriflunomide group, a difference of -0.11 (95% CI -0.16, -0.06). In trial 2, the odds ratio was 0.10 for ofatumumab and 0.25 for teriflunomide, the difference being -0.15 (95% CI -0.2, -0.09). The overall hazard ratio for worsening disability was 0.66 in favor of ofatumumab, and the hazard ratio for improvement of disability was 1.35 (95% CI 0.95-1.92) in favor of ofatumumab [7].

Autologous Hematopoietic Stem Cell Transplantation (AHHSCT)

Autologous hematopoietic stem cell transplantation (AHHSCT) is a new treatment modality being investigated for the treatment of multiple sclerosis (MS) and other diseases such as multiple sclerosis, Crohn's disease, and neuromyelitis optica (5.4). The principle behind AHSCT is to restore the immune system. Autologous peripheral blood stem cells were initially prepared using cyclophosphamide and filgrastim and collected for transplantation after ablation. After stem cell collection, autoreactive immune cells are removed using a full or partial myeloablative conditioning regimen that includes chemotherapy. Treatment options include cyclophosphamide (Cy) + antithymocyte globulin (ATG), Cy + alemtuzumab, or ATG + BEAM (carmustine, etoposide, cytarabine, melphalan) (5.4). After cooling, peripheral blood stem cells are reprogrammed to shorten the aplasia phase and generate a new immune system with more regulatory cell types and reduced pro-inflammatory T cell profiles. Early toxicities usually result from cytotoxic side effects and myelosuppression, but late toxicities are rare and may include infertility, viral reactivation (HSV, CMV, EBV), Secondary autoimmune disease, and myelodysplastic syndrome. Many retrospective studies, single-arm clinical trials, and case-control studies have evaluated the effectiveness of AHSCT and have shown promising results. In one meta-analysis, the estimated change in mortality was 2.1%, two-year morbidity was 17.1%, and five-year morbidity was 23.3%, with 83% of these patients being at 2 years. Patients with relapsing-remitting multiple sclerosis (RRMS) appears to have the best outcomes with the lowest mortality. Randomized controlled trials such as ASTIMS and MIST have shown that AHSCT is effective compared to conventional treatment (5.4). The MIST trial, a phase 3 crossover study, showed a 93% reduction in infection risk at 4-5 years in the AHSCT group compared with the medical modification (DMT) group. Although the results

of AHSCT are encouraging, they are associated with risks such as treatment-related mortality, late toxicity and disease progression, and secondary autoimmune disease. Ongoing Phase 2 and 3 studies have investigated the effectiveness of AHSCT compared to conventional treatments such as alemtuzumab, natalizumab, ocrelizumab, and rituximab. Currently, AHSCT appears to be a treatment for multiple sclerosis, especially as a one-time treatment, rather than long-term disease prevention. It may be most beneficial for younger patients with low disability, active liver disease, and few or no comorbidities. It is also important to consider cost-effectiveness, as AHSCT involves significant costs compared to traditional DMT. The long-term effects of early AHSCT on morbidity, morbidity, and mortality are currently being investigated [8].

Summary

Over the past three years, the range of treatment options for multiple sclerosis (MS) has expanded rapidly, along with the effectiveness of new drugs aimed at healing. Despite advances in understanding the biology of MS pathogenesis, there is still a lack of effective treatments for this progressive disease. Although disease-modifying therapies (DMTs) have been shown to be more effective in reducing relapse and MRI performance, they may also increase side effects due to disease prevention. Treatment of multiple sclerosis is difficult due to the heterogeneity of the disease, environmental and genetic effects, as well as genetic mutations and changes in the immune system over time and age. Interest in the development of neuroprotective and remyelinating therapies, including strategies that support mitochondrial function and cellular therapies targeting chronic pain, is encouraging. Various treatments have been investigated, including measures to improve immunity such as stimulating T cell function and promoting microglial function. To advance our understanding, it is important to conduct further research to identify early events associated with inflammatory states, early neurodegeneration, or both. Early treatment addressing the neuroinflammatory and neurodegenerative aspects of the disease, when used together, may be important in developing treatment strategies and achieving the ultimate goal of elimination in MS.

Neurorehabilitation in Multiple Sclerosis

Neurorehabilitation in Multiple Sclerosis (MS) is a holistic and collaborative approach involving various healthcare professionals to address the diverse symptoms associated with the disease [7]. It encompasses physical therapy to improve mobility, balance, and strength, occupational therapy for enhancing daily living skills, and speech-language pathology to address communication and swallowing issues. Cognitive rehabilitation targets memory, attention, and executive function deficits, while psychological support plays a crucial role in helping individuals cope with emotional challenges [7,8]. The personalized nature of neurorehabilitation recognizes individual needs, adapting interventions to specific symptoms, and aims to optimize function, mitigate disability, and improve the overall well-being of MS patients. Regular assessments ensure the ongoing effectiveness of the rehabilitation plan [8].

Physical Therapy

Tailored exercise programs are designed to improve strength, balance, and coordination. Aquatic therapy, gait training, and aerobic exercises have shown positive effects on mobility and fatigue in MS patients.

Occupational Therapy

Occupational therapists focus on enhancing daily life activities. Strategies may involve adaptive equipment, energy conservation techniques, and workspace modifications to empower individuals with MS to maintain independence.

Speech and Language Therapy

For those experiencing speech and swallowing difficulties, speech-language pathologists provide targeted interventions, including exercises and strategies to improve communication and manage swallowing challenges.

Cognitive Rehabilitation

Cognitive rehabilitation aims to address cognitive deficits such as memory loss, attention difficulties, and executive dysfunction. Personalized interventions may include memory training, cognitive exercises, and compensatory strategies (7.4).

Psychological Support

The emotional impact of MS is significant, and psychological support is essential. Counseling and psychotherapy help individuals cope with stress, anxiety, depression, and adjustment to life changes associated with the disease [7].

Conclusion

In conclusion, multiple sclerosis (MS) is a complex and heterogeneous disease with various clinical presentations, making its diagnosis and management challengin9. Recent advances in understanding the pathophysiology of MS have led to the development of new diagnostic techniques and therapeutic interventions. The availability of disease-modifying therapies (DMTs) has expanded, providing more options for patients with different forms of MS. Additionally, neurorehabilitation plays a crucial role in optimizing the

quality of life for individuals living with MS by addressing physical, cognitive, and emotional aspects. Ongoing research continues to explore novel treatment modalities and improve our understanding of the underlying mechanisms driving the disease. Collaborative efforts between healthcare professionals, researchers, and patients are essential for advancing knowledge and enhancing the overall care and well-being of individuals affected by MS [9].

References

1. Lublin FD, Reingold SC (1996) Defining the Clinical Course of Multiple Sclerosis: Results of An International Survey. Neurology 46(4): 907-911.

2. Hauser SL, Oksenberg JR (2006) The Neurobiology of Multiple Sclerosis: Genes, Inflammation, and Neurodegeneration. Neuron 52(1): 61-76.

3. Compston A, Coles A (2008) Multiple Sclerosis. The Lancet 372(9648): 1502-1517.

4. Kuhlmann T, Ludwin S, Prat A, Antel J, Bruck W, et al. (2017) An Updated Histological Classification System for Multiple Sclerosis Lesions. Acta Neuropathol 133(1): 13-24.

5. Ontaneda D, Thompson AJ (2017) Progressive Multiple Sclerosis. Handb Clin Neurol 149: 3-14.

6. Filippi M, Bar-Or A, Piehl F, Preziosa P, Solari A, et al. (2018) Multiple Sclerosis. Nat Rev Dis Primers 4(1): 43-49.

7. Ghasemi N, Razavi S, Nikzad E (2017) Multiple Sclerosis: Pathogenesis, Symptoms, Diagnoses and Cell-Based Therapy. Cell J 19(1): 1-10.

8. Surya N (2015) Rehabilitation of Multiple Sclerosis Patients in India. Ann Indian Acad Neurol 18(1): S43-S47.

9. Thompson AJ, Banwell BL, Barkhof F, Carroll WM, Coetzee T, et al. (2018) Diagnosis of Multiple Sclerosis: 2017 Revisions of the McDonald Criteria. Lancet Neurol 17(2): 162-173.