

Role of the Bruton Tyrosine Kinase Pathway in Multiple Sclerosis

HIGHLIGHTS

- › Addressing the Complex Pathology of Multiple Sclerosis
- › Exploring the Treatment Landscape and the Need for High-Efficiency Treatment
- › The Role of the BTK Pathway in the Mechanism of Disease

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OVERVIEW

This supplement to *The American Journal of Managed Care*® discusses the clinical course of multiple sclerosis and considers inhibition of the Bruton tyrosine kinase pathway to address additional aspects of the disease's complex pathophysiology.

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Role of the Bruton Tyrosine Kinase Pathway in Multiple Sclerosis

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Background

Multiple sclerosis (MS) is a chronic, immune-mediated, neurodegenerative disease that results in accumulation of neurologic disability over time. In the United States, it is estimated that nearly 1 million adults live with a diagnosis of MS.¹ This disease is 3 times more common in women than in men and is most prevalent in White and Black women, with lower incidence rates noted in Hispanic and Asian individuals.^{2,3} Compared with other racial groups, Black patients generally present with more severe forms of MS that progress more aggressively. This population is often underrepresented in clinical studies and is notably undertreated.⁴ Most patients are diagnosed with MS when aged between 20 and 50 years.² However, with the aging of the US population, the largest group of patients living with MS is now women aged 55 to 64 years.⁵ Overall lifespan decreases in patients with MS to a median of 75.9 years as compared with a median of 83.4 years ($P < .0001$) for matched controls.⁶

Clinical Burden

The course and clinical presentation of MS is heterogeneous. Patients with MS may experience symptoms such as pain and fatigue, as well as signs of neurologic dysfunction, including sensory and visual disturbances, motor impairments such as loss of mobility, and cognitive deficits.⁷ Initial presentation of symptoms is related to the location of the central nervous system (CNS) lesions.⁸ Due to the heterogeneity of MS symptoms, patients may initially present to a wide range of medical providers, such as primary care physicians, ophthalmologists, or orthopedic surgeons, delaying referral to a neurologist and the diagnosis of MS.⁸

Accumulation of disability in MS starts early, even before initial diagnosis.⁹ The FDA-designated tool used to assess disability in clinical trials is the Expanded Disability Status Scale (EDSS), which measures the impact of MS symptoms on functional areas: muscle coordination, ability to move, balance and coordination, bowel and bladder control, eyesight and eye movement, and thinking and memory. The EDSS is scored on a scale of 0 (normal) to 10 (death due to MS) in 0.5-point increments, where higher scores indicate

ABSTRACT

Multiple sclerosis (MS) is a chronic, immune-mediated, neurodegenerative condition that results in progressive accumulation of disability over the course of the disease. MS presents heterogeneously, and, as the disease progresses, patients develop a range of physical and neurologic problems that include reduced mobility, cognitive impairment, weakness, fatigue, pain, and defects in speech or vision. Economically, MS is costly, including both direct costs stemming from clinical care and medications and the indirect costs of productivity losses. These costs pose a substantial burden to patients, families, caregivers, employers, and society. There are 21 approved disease-modifying therapies for MS across several drug classes. The importance of early MS treatment has been confirmed, and progress has been made in the treatment of relapsing-remitting MS, although this progress has not been replicated for progressive presentations of the disease. Ongoing research continues to elucidate the exact mechanisms of disease in MS as well as potential new treatment strategies that may better address current gaps, such as disability progression in secondary progressive MS without activity. One of the novel pathways under investigation is the inhibition of Bruton tyrosine kinase, a cytoplasmic tyrosine kinase, which is expressed in B cells and other potentially targetable hematopoietic lineage cells. This review examines emerging hypotheses that targeting both B cells and myeloid cells within the periphery and central nervous system could yield clinical effects in key areas of MS pathophysiology that are currently unaddressed.

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For author information and disclosures, see end of text.

greater disability.¹⁰ The utility of the EDSS in clinical practice is limited by the time required to administer the test, the complexity of scoring, and its primary measurement of physical symptoms, such as ambulation.¹¹ Disability progression, as measured by EDSS score, has been confirmed across all forms of MS.⁹

Reduced mobility is the most common and obvious physical impairment in MS; however, as the disease progresses, the patient may experience multiple other problems, such as cognitive impairment, weakness, fatigue, pain, impaired bladder and bowel function, dysphagia, defects in speech/vision, and sexual dysfunction. Mental depression is more common in patients with MS than in the general population, and depression has been shown to be a strong predictor of reduced health status.^{6,12} Anxiety also affects a large proportion of patients with MS, and it can negatively impact patients' quality of life (QOL).¹³

As physical and cognitive impairments accumulate over time, people living with MS experience deterioration of physical and mental health status and QOL, which can affect employment status and family and other social relationships.^{12,14}

Social and Economic Burden

The interplay of physical disability and psychological impairment contributes to the lower rates of employment among people living with MS. Even at low levels of physical disability, unemployment levels among people living with MS suggest that the ability to work is affected early in the course of the disease.¹⁵ In response to a 2016 global survey, 39% of people living with MS reported being unemployed.¹⁶ Among this group, 82% cited MS as the reason for unemployment, with fatigue, mobility impairment, and weakness being the top symptom-related factors related to them not working. Among people with MS who were employed, 37% reported use of disease-modifying therapies (DMTs) as a factor that enabled them to stay at work.¹⁶

Cognitive deterioration occurs in approximately one-third of patients with MS within 3 years of diagnosis.¹⁷ Cognitive domains affected by MS may include speed in processing information, learning and retrieval (memory), attention, and executive function.¹⁸⁻²⁰ Cognitive dysfunction contributes considerably to unemployment, accidents, impairment of daily functions, and loss of social contacts.^{21,22}

MS poses economic burdens on the US health care system that are driven by a combination of direct costs of medical care and prescription drugs and indirect medical and nonmedical costs. The estimated total national economic burden of MS in 2019 was \$85.4 billion.²³

Direct costs of DMTs for MS have risen rapidly over the past decade, with implications for payers and patients. de Havenon and colleagues reported a retrospective analysis of Medicare Part D claims for neurologist-prescribed drugs from 2013 to 2017. They

found that neuroimmunology drugs, mostly drugs prescribed for MS, represented more than 50% of all payments but only 4.3% of claims. The payment per claim also increased by 46.9% from 2013 to 2017.²⁴

Between 2017 and 2020, the median cost increase was 5% across all MS DMT classes, including infused and oral therapies.²⁵ Results from a study of government-insured patients with MS in the United States show that, between 2010 and 2019, the median projected annual out-of-pocket cost for self-administered DMTs increased from \$5916 to \$6618.²⁶ These mounting costs pose a substantial burden to patients with MS, their families and caregivers, employers, and society in general.

Costs associated with MS care increase with worsening functional capacity.²⁷ Combined direct and indirect costs are at least twice as high in patients with severe disability than in those having mild disability, and direct costs tend to increase 2- to 3-fold as EDSS increases from 2.0 to between 4.0 and 6.5.²⁸⁻³⁰

Clinical Course of MS

The accumulation of disability in patients with MS correlates with progression through different clinical courses of the disease, which are defined as MS subtypes. In 2014, the International Advisory Committee on Clinical Trials in MS published definitions of the 4 subtypes of MS, based on assessments of disease activity and progression. Updates reflect clinical knowledge gained from MRI and other imaging techniques that were developed since the descriptions were first published in 1996.³¹

1. Clinically isolated syndrome

For many patients, MS begins with an episode of neurologic symptoms, either monofocal or multifocal, the extent of which can predict the progression of the disease. Some patients with an absence of MRI-detected lesions never progress to MS, and the episode remains classified as a clinically isolated syndrome (CIS).³²

2. Relapsing-remitting MS

Relapsing-remitting MS (RRMS), the most common course of the disease, is defined by episodes of new or increasing neurologic symptoms (relapses, exacerbations) followed by periods of partial or complete recovery from symptoms (remissions). During remissions, some symptoms may disappear, and/or some may continue and become permanent.³³ A relapse in MS is an inflammatory demyelinating event in 1 or more CNS locations occurring for at least 24 hours (without fever or infection) and resulting in noticeable symptoms and neurologic abnormality upon clinical examination.³⁴ During periods of remission, there is no apparent progression of the disease. RRMS is further characterized into 4 subtypes: (1) active, with relapses or signs of new MRI activity over time; (2) not active; (3) worsening, with progression; or (4) without progression, after a relapse.³³

3. Primary progressive MS

About 10% to 15% of patients experience primary progressive MS (PPMS), with a steady progression in neurologic disability from disease onset that typically does not feature periods of remission.^{31,35} Patients with PPMS experience worsening neurologic function and associated accumulation of disability from the onset of symptoms without early relapses or remissions. Like RRMS, PPMS can be either active (with occasional relapses or evidence of new MRI activity over a period of time) or inactive. PPMS also can present with progression, defined as evidence of disability accumulation over time, with or without relapse, or without progression.³³

4. Secondary progressive MS

Evidence from multiple studies shows that disability progressively worsens in secondary progressive MS (SPMS), either in the presence or absence of relapses. Some patients with RRMS develop progressive disease over time, transitioning from RRMS to secondary progressive MS.³¹ Typically, there is an “overlap” phase during which relapses still occur (relapsing SPMS, or active SPMS), followed by progression with no relapses (nonrelapsing SPMS [NRSPMS], or SPMS without activity).³⁶

Progressive MS is characterized by slow expansion of preexisting plaques.³⁷ Prior to the introduction of FDA-approved DMTs, it was generally agreed that a large portion of patients with MS converted to SPMS within 2 decades of disease onset.³⁸ However, utilization of DMTs has decreased the rate of conversion to progressive disease. The results of an international, observational cohort study of patients with MS indicate that those who initially receive second-generation DMTs within 5 years of disease onset are significantly less likely to convert to SPMS than are those treated with first-generation drugs.³⁹

There is ongoing interest in continued refinement of MS phenotypes. One hypothesis suggests that MS progresses along a continuum from relapsing to progressive MS, with differences in presentation attributable to changing levels of neurologic reserve as patients age.⁴⁰ Neurologic reserve refers to compensatory or protective brain function in response to adverse events such as stressors or disease.⁴⁰ During the early, inflammatory phase of MS, most manifestations of the disease are subclinical, and symptoms may be buffered if a patient has adequate neurologic reserve. However, brain volume loss due to neuronal damage begins early, regardless of MS phenotype.⁴¹ As brain loss continues, the patient’s neurologic reserve is depleted more rapidly by the combined effects of aging and disease processes. As this occurs, patients may enter the progressive stage of MS, where the impact of the disease on cognitive function becomes more apparent. Vollmer and colleagues suggest that an individual patient’s level of neurologic reserve, which correlates with duration of disease and age, may explain why some patients with MS develop progressive disease and others do not.^{40,42} Treating as early as possible with a highly effective and acceptably safe DMT

could address the goal of minimizing neuronal loss and preserving neurology reserve to avoid entering a progressive phase of MS and to buffer against the effects of normal aging.⁴⁰

Addressing the Complex Pathology of MS

Although multiple therapeutic options are available, many address only limited aspects of MS pathophysiology. Current therapies modulate the immune adaptive response, but they do not inhibit innate immune cells (eg, microglial cells, macrophages, and dendritic cells) that participate in the progression of MS.⁴³

Both the adaptive immune system (composed of B cells and T cells) and the innate immune system (composed of microglia and macrophages) have a role in MS pathogenesis, and both represent potential targets for the treatment of progressive MS.^{44,45} The innate immune system plays a critical role in a healthy, inflamed, injured, and recovering CNS.⁴⁶ A goal for future treatment of MS could be early, simultaneous targeting of peripheral nervous system (PNS)-intrinsic and CNS-intrinsic inflammation, with the goal of modulating these 2 immunologic arms of the disease to theoretically provide neuroprotection or antineurodegenerative therapy.⁴⁷

Treatment Landscape

At the time of this publication, 21 DMTs are available for MS across several drug classes.⁴⁸ The primary goal of treatment with DMTs is to reduce the occurrence of relapses and the formation of new CNS lesions.⁴⁹

DMTs with different mechanisms of action are available in formulations with varying routes of administration to slow disease progression and slow the accumulation of disability. DMTs can limit the occurrence and severity of relapses and can help prevent the irreversible CNS damage that can lead to increased disability and progressive disease.⁴⁸

Use of DMTs delays disability accrual, which begins early in the disease. A recent United Kingdom study analyzed data of more than 27,000 patients with MS, with up to 15 years of follow up.⁹ The goals were to identify (1) the role of clinical relapses in driving the worsening of disease, and (2) the extent to which DMTs can prolong the time to accumulation of milestone disability levels, as measured by EDSS.⁹ Results showed that DMTs reduced the proportions of patients who experienced relapse and of patients who experienced all-cause disability-worsening events. The strongest treatment effect was seen in patients with RRMS.⁹

The considerable progress made in the treatment of RRMS in the past 2 decades has not been replicated for progressive forms of MS that do not respond to DMTs.⁵⁰ Controlled clinical studies have provided pivotal evidence for a therapeutic benefit of immune- and inflammatory-targeted treatments, but this effect, mainly seen in patients in the early stages of the disease, is limited, particularly in ameliorating the progression of clinical deficit.⁵¹

There is growing evidence that inflammation is not the major cause of disability in progressive MS; instead, this disability may be driven by presymptomatic neurodegeneration.⁵¹ This suggests that existing treatments may not be targeting the correct mechanism of disease in progressive MS and that different approaches to treatment are needed.⁵²

Need for Early High-Efficacy Treatment

Consensus recommendations affirm the importance of early initiation of MS treatment.^{35,53} Important goals of early treatment are to minimize axonal damage, a key determinant of irreversible disability, and to help minimize disease activity in the early relapsing phases, which is predictive of long-term disability.⁵⁴

Early initiation of MS treatment with high-efficacy DMTs may be more effective than is escalation from less-effective treatments. In a longitudinal prospective study conducted in the United Kingdom, 5-year disability outcomes among 592 patients favored use of induction therapy vs escalation treatment with high-efficacy DMTs. The early intensive treatment group experienced a change in EDSS scores of +0.3 at 5 years, whereas the higher-efficacy DMT group had an increase of 1.2. The first-line treatment strategies for these 2 groups were high-efficacy treatments and moderate-efficacy therapies, respectively.⁵⁵

Investigators of a multinational, prospective cohort study in 2017 sought to determine the association between the use, type, and timing of DMTs with the risk of conversion to SPMS. The results affirmed several key principles that underline the importance of early treatment. Treatment with any DMT reduced the risk of conversion to SPMS, although risk of conversion after initial treatment with highly effective DMTs was lower than with other DMTs. The study also showed that the risk of conversion was lower for patients who received early treatment than for those who received late treatment.³⁹

Considerations of Treatment Selection

There is a lack of consensus among guidelines set forth by the American Academy of Neurology (AAN), the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) and the European Academy of Neurology (EAN), and the Consortium of MS Centers (CMSC) around treatment decision-making and selection. Specifically, approaches differ regarding asymptomatic patients who are between relapses, patients with CIS, and patients with NRSPMS.

The 2018 ECTRIMS/EAN guidelines have limited recommendations on SPMS and do not explicitly mention NRSPMS. The guidelines cite weak evidentiary support of treatment of patients with active SPMS.³⁵ Discussion of SPMS in the 2018 AAN guideline is limited to recommendations for stopping DMT, focusing primarily on the benefit of DMT for people with SPMS who have relapses or MRI-detected new lesion formation. The guidelines note that relapses are associated

with more rapid disability progression but tend to occur in patients younger than 55 years and earlier in the disease course.⁵⁶

The 2022 CMSC Practical Guidelines include a more comprehensive discussion of DMT use in SPMS. The guidelines advise changing or escalating therapy if patients have disease activity during SPMS and acknowledge that therapies are needed that address the degenerative neurologic mechanisms in progressive MS and that are distinct from the primarily anti-inflammatory approaches used today.⁵³

Bruton tyrosine kinase (BTK) inhibitors are an emerging type of DMT for MS; many of these agents are being tested in clinical trials globally for relapsing, primary, and secondary progressive MS. These drugs were initially brought to market as immunomodulatory cancer treatments, but they have since been recognized for their potential to treat MS more effectively than do existing DMTs. BTK inhibitors prevent brain damage through selective B-cell targeting and crossing of the blood-brain barrier (BBB), a border of cells in the brain and spinal cord that current DMTs cannot access.⁵⁷

Role of the BTK Pathway in the Mechanism of Disease

BTK, a cytoplasmic tyrosine kinase, is expressed in B cells and in hematopoietic lineages including monocytes, macrophages, microglia, mast cells, and neutrophils.^{44,58} The BTK pathway is potentially targetable, as it is involved in the MS mechanisms of disease and is expressed in multiple immune cells essential to MS pathophysiology.⁴⁴

BTK is an effector molecule with critical involvement in many aspects of B-cell development, including proliferation, maturation, differentiation, apoptosis, and cell migration.⁵⁹ In B cells, BTK is located downstream of the B-cell receptors and is essential at various stages of B-cell development.⁵⁸ BTK is also involved in other signaling pathways in B cells, including the chemokine receptor, toll-like receptor, and Fc receptor signaling.⁵⁸ In a mouse model, BTK deficiency was associated with reduced B-cell numbers, and the remaining B cells showed reduced survival attributable to defective activation of the transcription factor NF- κ B.⁶⁰

BTK plays a role in both adaptive and innate immunity, which are central to MS pathophysiology across the BBB.^{61,62} In animal models, BTK has been successfully delivered to both PNS and CNS cells, confirming that inhibition of BTK can successfully penetrate the BBB.⁶³

BTK is highly expressed in microglia within lesion tissue from patients with progressive MS.⁶⁴ Microglia in MS lesions strongly express Fc γ R1, and preclinical studies have demonstrated the importance of the microglial Fc γ R pathway in antibody-mediated demyelination.^{65,66} Activated BTK is a mediator of proinflammatory signals, such as overexpression of inflammatory cytokines (ie, tumor necrosis factor [TNF] and interleukin [IL]-1B) that are

associated with the inflammatory response.⁶⁷ The production of IL-6 and IL-10 is also regulated by BTK in immune cells; in mast cells, degranulation and TNF production are BTK-dependent.⁶⁸ Additionally, BTK has an important role in the full expression of FcεR signal transduction in mast cells and basophils.^{60,68}

The BTK pathway has targets in both the adaptive and innate arms of the immune system; these targets cause damage both in the PNS and CNS.⁶² By targeting multiple biological processes that include B-cell and macrophage activation, the BTK pathway may potentially mitigate disease activity across the spectrum of MS.^{45,69}

Inhibition of BTK has been shown to reduce both in vitro and in vivo expression of the regulator of G-protein signaling 1 (RGS1) gene, which is implicated in chemokine receptor signaling in adaptive immune cells.^{64,70} A novel model of immune-mediated cortical demyelination using recombinant antibodies derived from patients with MS and human complement (MSrAb+huC) showed that microglia migrate to the site of demyelination and engulf myelin; the model further demonstrated that BTK inhibition with PRN 2675* reduced this migration and engulfment in real time, preventing cortical oligodendrocyte loss.⁷¹

Research about the inhibition of the BTK pathway is fueling clinical development of agents targeting different B-cell-related targets of interest in MS. While anti-CD20 monoclonal antibodies are among the most effective and studied B-cell-targeted therapies in MS, long-term depletion of B cells puts patients at risk of infectious complications. Ongoing research on more functionally restricted pathways (eg, BTK inhibition) that target both B cells and myeloid cells in the PNS and CNS may be a novel strategy for addressing multiple mechanisms of MS.

Conclusions

Currently approved therapeutic options available to patients with MS address only limited aspects of MS pathophysiology. DMTs can reduce relapse rates, but patients' unmet needs include ways to halt disability accumulation and to improve disability. Disability and neurodegeneration can continue to progress despite a reduction in relapse rates, and there are limited options for patients with progressive MS phenotypes. Ongoing research on MS pathophysiology continues to shed light on the complex interactions among B cells, T cells, and myeloid cells, which research points to alternative targets for treatment. Research on the expression of BTK in immune cells that are essential to MS pathophysiology suggests that BTK inhibition may be effective in dysregulating mechanisms of adaptive and innate immunity in MS, which points to potential new ways to address additional dimensions of the complex pathophysiology of MS in multiple CNS regions. ■

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