Review

Role of Bruton's Tyrosine Kinase (BTK) in the Treatment of Cognitive Impairment in Patients with Multiple Sclerosis

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Review

Role of Bruton's Tyrosine Kinase (BTK) in the Treatment of Cognitive Impairment in Patients with Multiple Sclerosis

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Abstract: Multiple sclerosis (MS) is a persistent inflammatory disease affecting the central nervous system. Bruton's tyrosine kinase (BTK) is an enzyme crucial in the communication process of B cells, which have a significant impact on the development of MS. Recently, BTK inhibitors have emerged as a promising treatment strategy for MS due to their ability to modulate the immune system. In this study, an extensive literature search was performed utilizing multiple databases, such as PubMed, Embase, and Scopus to examine the potential use of BTK inhibitors in managing cognitive disorders experienced by individuals with MS. We found that BTK inhibitors targeting microglia offer potential advantages for managing neurodegeneration associated with cognitive impairments in MS patients by slowing down degeneration processes effectively. Their ability to impact microglial function and penetrate the CNS positions them as promising candidates for improving cognitive function. This study suggests that BTK inhibitors provide new possibilities for managing inflammatory and neurodegenerative phases of MS through their effects on microglia activation pathways. Further research and clinical trials are necessary to fully explore their efficacy in treating MS while addressing barriers related to cognitive impairment.

Keywords: Bruton's tyrosine kinase (BTK); cognitive disorders; multiple sclerosis (MS); Neuroinflammation; immune system

1-. Introduction

Hematopoietic cells, including B cells, myeloid cells, and platelets (excluding T and plasma cells), predominantly exhibit the expression of Bruton tyrosine kinase (BTK). The discovery of BTK's involvement in X-linked agammaglobulinemia (XLA) marked its initial identification in disease pathogenesis [1, 2]. XLA is an inherited immunodeficiency disorder caused by mutations in the BTK gene. These mutations reduce the number of B cells, rendering the patient more vulnerable to infections[2]. The BTK gene is located on the X chromosome within the Xq21.3-22.1 region. It encodes for a 76 kDa polypeptide consisting of 659 amino acid residues[3].

BTK plays a crucial role in intracellular signaling pathways in both B cells and myeloid cells, including monocytes and macrophages[4]. It is involved in the maturation and differentiation of B cells into memory B cells and plasma cells. Once B cells undergo these changes and complete their maturation, BTK becomes inactive and loses its function[5]. Inhibition of BTK results in the disruption of DNA synthesis and selectively induces apoptosis in B cells. This approach emerged as a promising unique therapeutic target in the treatment of hematological malignancies, including B lymphocyte leukemia[6]. In the late 20th century, Mahajan et al. developed the first BTK inhibitor, initially named LFM-A13, which exhibited synergistic anti-leukemia effects in combination with ceramide or vincristine in laboratory experiments [7].

Ibrutinib, the first-generation drug with BTK inhibitory potential, is a small but potent molecule that irreversibly inhibits the function of BTK[8]. One of its significant advantages is eliminating the necessity for chemotherapy in patients[8, 9]. Ibrutinib, also known as PCI-32765, has

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gained approval for the treatment of chronic lymphoid leukemia (CLL), mantle cell lymphoma (MCL), and Waldenstrom macroglobulinemia[3].

Certain side effects have been associated with ibrutinib use, including bleeding, skin lesions, gastrointestinal symptoms, and atrial fibrillation[10-15]. In addition to the development of resistance to ibrutinib, the significant side effects associated with its use have prompted the development of next-generation BTK inhibitors[9, 16], including acalabrutinib, zanubrutinib, tirabrutinib, and orelabrutinib. Recognizing the role of BTK in modulating B cell differentiation, efforts have been made to explore the potential of these inhibitors in the treatment of autoimmune diseases. B cells play a crucial role in the pathogenesis of rheumatoid arthritis (RA) through mechanisms including antibody production, antigen presentation to T cells, and activation of the complement system[17].

In the context of studying BTK inhibitors for RA, the outcomes have been mixed. Out of nine clinical trials conducted in this field, four of them (involving BMS-986142, branebrutinib, polsetinib, and spebrutinib) reported unsatisfactory results. However, there is one medication, fenebrutinib, that has shown promising outcomes in the treatment of RA)[3, 18].

Systemic lupus erythematosus (SLE) is another disease of interest when evaluating BTK inhibitors. Studies have focused on the critical role of B cells in the development of SLE[19]. In clinical trials for SLE, four drugs were investigated: branebrutinib, eslubrutinib, evobrutinib, and fenebrutinib. However, evobrutinib and fenebrutinib had no significant effects on SLE [17, 20, 21].

2.- The Role of Bruton's Tyrosine Kinase (BTK) in Multiple Sclerosis

Dysregulation of the BTK pathway and overexpression of this molecule in B cells contribute to the proliferation of B cells. This dysregulation of B-cell differentiation can lead to the development of autoimmune disorders, including multiple sclerosis (MS)[22]. In the context of MS, elevated levels of BTK have been detected in B cells and microglia in patients with relapsing-remitting MS (RRMS) and secondary progressive MS (SPMS)[23, 24].

Indeed, BTK expression in macrophages and microglia suggests that the discussed drugs can affect the innate immune system in addition to B cells[25]. It is worth noting that these drugs primarily modulate B-cell activity rather than causing extensive and permanent elimination[26, 27].

Microglia, the largest population of cells in the central nervous system (CNS), have been found to play a significant role in promoting disease progression in patients with (MS) by activating neurotoxic pathways and inflammatory factors[28]. However, it is important to note that microglia also exhibit evidence of neuroprotective and anti-inflammatory effects. This dual activity of microglia has made them a popular focus of research[29].

Microglia play a crucial and multifaceted role in CNS development, immune surveillance, and repair. Their involvement in MS is complex and encompasses various dimensions. Evidence reveals that microglia influence both demyelination and remyelination processes in MS[30]. In early RRMS, microglia are present in acute MS lesions along with the B cells, macrophages, and T cells[31, 32].

The exact mechanisms underlying brain atrophy in patients with MS are not fully understood. However, it is known that volume loss in the grey matter is associated with cognitive impairment. In a study utilizing PET scans, the role of microglia activation in the grey matter and its relationship with brain atrophy and disability in MS patients was investigated. The result of the mentioned study revealed that microglia activation in the subcortical grey matter was higher in SPMS compared to RRMS and the healthy population. Furthermore, microglia activation in the thalamus was linked to atrophy and disability. These findings suggest that microglia play a crucial role in the progression of MS[33]. Therefore, BTK inhibitors may disrupt the function of these cells and alter the course of the disease.

Indeed, MS can be divided into two distinct phases: the inflammatory phase and the neurodegenerative phase. Current drugs available for MS treatment are generally more effective in targeting the inflammatory phase, while the degenerative phase remains challenging due to limited treatment options. This has led to the exploration of novel drugs targeting mechanisms involved in neurodegeneration. Additionally, a crucial consideration in the design of these new drugs is their

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ability to cross the blood-brain barrier (BBB). Many existing medications do not possess this capability, which can limit their efficacy in addressing the neurodegenerative aspects of MS[34].

BTKis possess two notable features. Firstly, they exhibit effectiveness not only on B cells but also on microglia, which play a crucial role in the progression, disability, and brain atrophy associated with MS, as mentioned earlier. Secondly, these drugs can cross the BBB and access the CNS. These two characteristics raise hopes for their efficacy in managing the neurodegenerative aspects and overall progression of MS, beyond just the inflammatory phase. Additionally, a range of BTKi variations is currently undergoing large-scale clinical trials for the treatment of MS. These drugs exhibit significant differences in their pharmacological properties, including selectivity, reversibility, and CNS penetration[35] Notable BTKis developed for MS treatment include evobrutinib, tolebrutinib, fenebrutinib, remibrutinib, and orelabrutinib. Among them, evobrutinib is an orally administered agent acting as a covalent BTK inhibitor and is associated with fewer complications compared to ibrutinib[16] It is important to note that BTK inhibition is reversible after discontinuation[36, 37].

The efficacy and safety of evobrutinib have been examined in three phase II trials conducted for MS, RA, and SLE. In the MS trial, the drug demonstrated a significant reduction in T1 gadolinium enhancement (T1 Gad-lesion) compared to the initial condition, although it did not have a significant impact on the ARR or disability progression [21, 38-40]. The Phase II clinical trial revealed a dose-dependent reduction in slowly expanding lesions (LSEs) after 12 months [41]. Moreover, the drug was well-tolerated in the MS assay, showing no serious adverse effects. Although the open-label extension (OLE) phase of the MS trial is still ongoing, preliminary data indicate that the drug's safety profile has been maintained for more than two years[40, 42].

Tolebrutinib is an orally administered medication that specifically and permanently blocks the activity of BTK and has a strong ability to enter the CNS[43]. During Phase IIb trials, administering a high dosage of tolebrutinib resulted in a decrease in new T1 Gad+lesions and T2 lesions. Currently, there is an ongoing evaluation of this drug through an extensive Phase III clinical trial. Another oral BTK inhibitor called fenebrutinib is being studied in Phase II clinical trials for patients with RA and SLE and has shown effectiveness [44, 45].

Based on the safety findings from studies in other autoimmune disorders, three phase III trials have been initiated for MS. One of these studies, called FENtrepid (NCT04544449), includes patients with primary progressive MS, and the comparison group will receive either a placebo or ocrelizumab. The main focus of this study is to measure the time it takes for confirmed disability progression (CDP) to occur over a period of 12 weeks. Additionally, there are ongoing studies assessing the effectiveness and safety of two other drugs, namely Remibrutinib and Orelabrutinib. The results of these studies will be determined in the upcoming years[46-50].

3.- Cognitive disorders in multiple sclerosis

MS patients frequently experience cognitive impairment (CI), with a prevalence ranging from 45% to 70%. This CI can significantly impact various aspects of patients' lives, including their daily activities, vocational status, personal relationships, and overall quality of life[51]. It is important to note that cognitive disorders in patients with MS do not exhibit a consistent pattern[52]. However, certain cognitive domains are commonly affected, including information processing speed (IPS), working memory, visuospatial ability, executive functions, and complex attention [51]. On the other hand, the occurrence of dementia in patients with MS is less frequent, affecting approximately 5% of individuals[53].

CI has been reported in all types and stages of MS [54]. It can be identified even in the early stages of MS, including Radiologically Isolated Syndrome (RIS) [51]. Interestingly, CI does not correlate with the Expanded Disability Status Scale (EDSS) score in all cases of MS [55, 56]. On the other hand, there is a proven correlation between CI and magnetic resonance imaging (MRI) data in MS. However, the presence of MRI lesions can only explain a portion of the observed cognitive impairment [57].

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The exact causes of cognitive dysfunction in MS are not fully understood [58]. Nevertheless, existing data indicate that the underlying mechanisms are intricate and involve a combination of factors, including damage to both white and gray matter in the brain [59, 60]. To address cognitive impairments in MS, various approaches have been employed, including cognitive rehabilitation, cognitive-behavioral therapy, and pharmacological interventions [61].

Gray matter lesions and brain atrophy are considered the primary pathological mechanisms observed during the progression of MS. These mechanisms can result in clinically significant cognitive impairment in approximately half of the individuals diagnosed with MS[62]. Tissue damage and atrophy in the brain are associated with both the duration of the disease and the efficiency of cognitive networks [62, 63]. Certain cognitive domains are more frequently affected in MS, including episodic memory, information processing efficiency, executive function, and attention [62, 64, 65].

Neuronal degeneration, inflammation, and the development of lesions may contribute to cognitive impairment in individuals with MS [66].

Cognitive dysfunction in MS may occur due to the disruption of essential cognitive processing areas caused by damage to the connecting white matter[59]. Studies utilizing brain imaging methods have shown an association between cognitive impairment in MS patients and a decrease in brain volume or brain atrophy[64].

4.- The effects of disease-modifying drugs on cognitive impairment of MS patients

There is evidence suggesting that disease-modifying drugs (DMDs) have beneficial effects on the cognitive function of individuals with MS. Approved DMDs for MS have been shown to help prevent the formation of brain lesions and reduce brain atrophy. Research has found an association between brain lesions and cognitive function, indicating that DMD therapy provides a compelling rationale for preserving normal brain function in MS patients[67, 68].

The complete understanding of how DMDs affect cognitive function remains limited due to a lack of extensive trials in this area [67]. Moreover, the methodology used in existing studies has its limitations, including small sample sizes of MS patients with varying clinical conditions, absence of randomization, use of different cognitive assessment tools, and failure to consider the patients' cognitive performance at the beginning of the study. Consequently, these studies do not provide a definitive and unified conclusion on the effectiveness of DMDs in enhancing the cognitive abilities of MS patients[69]. However, a meta-analysis and systematic review conducted by Landmeyer et al. in 2020 shed some light on this matter. Their findings indicate that DMDs have a mild to moderate positive impact on the cognitive function of individuals with relapsing-remitting MS [70].

A recent study conducted by Harel et al. in 2019 examined the cognitive function of individuals with RRMS and SPMS who had been receiving DMDs for almost 20 years. The study involved a large cohort and found that the use of DMDs significantly altered the progression pattern of MS. A considerable proportion of MS patients treated with DMDs did not experience significant cognitive decline, which could negatively impact their quality of life, despite the long duration of the disease[68]. However, it should be noted that the effects of different DMDs on cognitive performance may vary, and patients in the study had switched between various DMDs over the course of the long-term study. Therefore, the observed beneficial effects could not be attributed solely to a specific DMD. In a review article from 2018, the effectiveness of different DMDs in enhancing cognitive abilities among patients with MS were examined separately. The article suggested that Interferon beta-1a, Interferon beta-1b, Glatiramer acetate, and Natalizumab may have a role as cognitive enhancers for individuals with MS[53]. Another study by Amato et al. in 2020 focused on the effects of dimethyl fumarate (DMF) on cognitive impairment in RRMS patients. This single-arm study showed that a 2-year treatment with DMF could slow down the rate of cognitive decline and improve quality of life [71].

In a study conducted by Salehizadeh et al. in 2022, the effect of Rituximab on CI in individuals with SPMS was analyzed. The results of the study suggest that Rituximab may have a positive impact on the cognitive dysfunction experienced by SPMS patients[72]. Furthermore, a systematic review

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examining the effects of Ocrelizumab on MS progression indicated that Ocrelizumab, in addition to its strong anti-inflammatory properties, might have the potential to limit disability progression and potentially provide beneficial effects on cognitive function[73].

Patients with SPMS and primary progressive MS (PPMS) generally experience a more pronounced cognitive decline[53]. Cognitive impairment is a prevalent symptom of PPMS, and its severity in PPMS patients can be greater than in patients with RRMS[74]. Ocrelizumab is the only DMD approved by the FDA for the treatment of PPMS[75]. However, based on current knowledge, there is a lack of substantial evidence regarding the beneficial effects of DMDs in reducing cognitive impairment among PPMS patients.

Although studies highlighting the positive effects of disease-modifying therapies (DMDs) on cognitive performance in MS patients are increasing, there are limitations to their use for treating cognitive dysfunction. DMDs have been successful in reducing cognitive decline, but they are not highly effective in directly treating cognitive dysfunction [76]. Furthermore, the beneficial effects of these therapies on cognitive impairment are relatively modest, as evidenced by meta-analyses showing only a weak improvement in cognitive tests [69, 70]. Additionally, as mentioned earlier, the existing studies in this area have methodological limitations preventing firm conclusions. Given the high prevalence of cognitive disorders in MS patients, there is currently a need to identify more effective treatments for cognitive impairment that go beyond merely preventing further decline and can be prescribed across different types of MS.

5.- Breaking the barrier: understanding the resistance of cognitive disorders in MS patients to treatment response

Even though disease-modifying therapies (DMTs) have made significant progress in reducing relapses and physical disability in patients with MS, effectively managing cognitive impairment continues to be a challenging task[77].

Resilience to treatment is a characteristic of cognitive decline in MS. While other MS symptoms typically show improvement or vanish with proper therapy, cognitive impairments tend to endure or deteriorate despite adequate disease management[78]. This resistance represents a significant obstacle in clinical practice, underscoring the importance of gaining a more comprehensive understanding of the underlying mechanisms responsible for this impaired response to treatment[79].

Several factors have been proposed to explain the resistance of cognitive disorders in patients with MS to treatment response. Sumowski et al. (2018) emphasize the importance of developing theoretical models of MS-related cognitive dysfunction and identifying mechanisms of action to address these deficits [80].

A major factor contributing to the challenge is the complex nature of cognitive impairment in MS, which involves multifocal and diffuse brain pathology[80, 81]. Unlike localized neurological deficits, cognitive function relies on intricate networks that span multiple brain regions[82]. The extensive demyelination, loss of axons, and atrophy of gray matter observed in MS disrupt these networks, creating a challenge in targeting specific areas for therapeutic intervention[77]. Furthermore, the precise pathological mechanisms responsible for cognitive impairment in MS are not fully understood. Inflammation, oxidative stress, excitotoxicity, and synaptic dysfunction have all been identified as factors contributing to the development and progression of cognitive deficits[83]. Nevertheless, the precise functions and relationships of these elements remain unclear. Deciphering the intricate processes involved in cognitive decline related to MS is crucial in pinpointing possible avenues for treatment[84].

Another important aspect to consider is that existing therapies for cognitive decline in conditions like MS primarily concentrate on the immune system rather than directly addressing the underlying brain pathology. However, cognitive impairment stems from damage to the brain itself, necessitating interventions that specifically target these cerebral issues and demonstrate effectiveness. It is crucial to acknowledge that cognitive dysfunction in MS arises from various mechanisms, including neuronal damage, disruption of synaptic connections, and neuroinflammatory processes within the

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central nervous system. Current treatments primarily focus on modulating immune responses and reducing inflammation, but they may not adequately address the specific brain-related factors contributing to cognitive impairment. To effectively manage cognitive deficits, it is imperative to develop drugs or therapies specifically designed to target brain pathologies associated with impaired cognition. These interventions should aim to preserve neuronal function, promote neuroplasticity, enhance the formation and maintenance of synapses, and potentially facilitate the repair of myelin.

By changing the way, we treat patients with MS or similar neurological disorders, focusing on addressing the brain abnormalities that cause cognitive impairment, we can potentially improve the effectiveness of therapy and enhance the overall quality of life for these patients. It is crucial for future research to prioritize the development of new medications or novel strategies that specifically target cognitive dysfunction linked to brain-related problems.

To sum up, the current treatments for conditions including MS-related cognitive impairments primarily focus on immune modulation rather than directly addressing brain pathology. However, there is an increasing demand for therapeutic approaches that specifically target the cerebral abnormalities responsible for cognitive deficits. These targeted interventions show potential to improve treatment effectiveness and ultimately enhance patient outcomes. Another important factor to consider is the diversity of cognitive impairment in MS. Patients exhibit significant variations in the nature, severity, and progression of cognitive deficits. This heterogeneity can be attributed to individual differences in genetic susceptibility, disease subtype, lesion location, and compensatory mechanisms[85].

By identifying different subgroups of patients with unique cognitive profiles and treatment response patterns, interventions can be personalized to better meet individual needs, resulting in improved outcomes[86]. Moreover, it is crucial to consider the impact of factors unrelated to MS on cognitive decline and the effectiveness of treatments. The presence of concurrent mental health disorders like depression and anxiety can exacerbate cognitive deficits and impede the success of therapy [87]. Furthermore, lifestyle elements including exercise, diet, sleep habits, and cognitive reserve can affect cognitive function and the response to treatment. It is essential to gain a more profound comprehension of how these factors influence cognitive impairment in MS to develop comprehensive treatment approaches that encompass the complete spectrum of influences[88].

Due to the substantial impact of cognitive impairment on the overall well-being and functional capabilities of people with MS, it is crucial to urgently address the underlying mechanisms that hinder its treatment response. Benedict et al. (2020) thoroughly explore the treatment of cognitive impairment in individuals with MS and emphasize the lack of substantial evidence supporting the efficacy of medications specifically designed to alleviate cognitive impairment in these patients[81]. By understanding the root causes, medical professionals and scientists can develop new and creative treatments to reduce cognitive problems and improve the well-being of patients. This endeavor is crucial for meeting the needs of people living with MS and offering them effective interventions that specifically tackle cognitive challenges.

6-. How may BTKIs impact barriers to cognitive impairment?

Cognitive impairment is a highly consequential symptom of MS that greatly affects the daily life and social engagements of patients. In MS, there are widespread lesions found in both the white matter and grey matter, which can be visualized using MRI. Even brain matter that appears normal (NAWM) is affected[89]. Cerebral atrophy, characterized by the shrinking of the brain, begins early in the course of MS and progresses at a rate of approximately 0.5-1.35% per year [90, 91].

During the initial stages of MS, inflammation plays a prominent role in the development of brain atrophy. However, as the disease progresses, additional factors contribute to this process. These include the activation of microglia (a type of immune cell in the brain), inflammation of the meninges (the protective membranes surrounding the brain and spinal cord), deposition of iron, oxidative stress, and diffuse axonal injury in the normal-appearing brain matter (NAWM)[92]. Cognitive impairment may be present in the early stages of the disease[93]. Cortical atrophy, the shrinking of the outer layer of the brain, is considered a predictor of cognitive impairment[94]. To gain insight

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into the underlying mechanisms of neurodegeneration and cortical atrophy, it is helpful to examine the dual role of microglia [95].

A PET survey conducted on MS patients revealed a connection between heightened activity of cortical microglia, cortical atrophy, and cognitive function [96]. Microglia play a dual role in either promoting neuroprotection or contributing to neurodegeneration by influencing synaptic pathways, releasing or inhibiting inflammatory factors and cytokines, and releasing glutamate [95].

Current MS medications do not appear to be significantly effective in improving or halting the progression of cognitive impairment. One possible explanation for the limited impact of these drugs on cognitive impairment is their insufficient inhibitory effect on the innate immune system, including microglia. Additionally, their limited ability to cross the BBB may hinder significant effects on neurodegeneration in MS. As a result, research efforts have focused on developing drugs with enhanced penetration into the CNS.

Given the considerable impact of microglia, there is optimism that BTKi, targeting these cells, may provide advantages in neurodegeneration. If the progression of neurodegeneration can be slowed down and improved, it is hoped that cognitive impairments may also be alleviated. Consequently, drugs with neuroprotective properties may potentially have positive effects on cognition. BTK inhibitors are intriguing medications that possess two reported characteristics: their impact on microglia and their ability to penetrate the CNS. Therefore, it is conceivable that, in addition to controlling the inflammatory phase, they may also influence the neurodegenerative phase and improve cognitive impairment[97].

6-. Conclusion:

In conclusion, dysregulation of the BTK pathway and overexpression of BTK in B cells have been implicated in the development of autoimmune disorders, including multiple sclerosis (MS). Elevated levels of BTK have been detected in B cells and microglia in patients with MS. Microglia, which play a significant role in promoting disease progression, exhibit both neurotoxic and neuroprotective effects. Evidence suggests that microglia influence demyelination and remyelination processes in MS. Furthermore, microglia activation has been linked to brain atrophy and disability in MS patients.

Current drugs for MS primarily target the inflammatory phase and have limited efficacy against neurodegeneration. The exploration of novel drugs targeting mechanisms involved in neurodegeneration is crucial. BTK inhibitors possess two notable features: their impact on both B cells and microglia, as well as their ability to cross the blood-brain barrier (BBB) and access the central nervous system (CNS). These characteristics raise hopes for their effectiveness in managing the neurodegenerative aspects and overall progression of MS.

Several BTK inhibitors are currently undergoing clinical trials for the treatment of MS. Evobrutinib has shown a reduction in gadolinium-enhancing lesions but did not significantly impact disability progression. Tolebrutinib specifically blocks BTK activity permanently and exhibits strong CNS penetration capabilities. Fenebrutinib also shows promise based on studies conducted on other autoimmune disorders.

Cognitive impairment is a significant symptom of MS that greatly affects patients' daily life. Neurodegeneration plays a prominent role in cognitive impairment, with cortical atrophy considered a predictor of cognitive decline. Current medications have limited impact on cognitive impairment due to insufficient inhibitory effect on microglia activity and poor BBB penetration.

BTK inhibitors targeting microglia hold potential advantages for addressing neurodegeneration associated with cognitive impairments seen in MS patients. By slowing down neurodegeneration, these medications may also alleviate cognitive impairments. The ability of BTK inhibitors to impact microglia and penetrate the CNS makes them promising candidates for improving cognitive function in MS.

In conclusion, BTK inhibitors offer a new avenue for managing both the inflammatory and neurodegenerative phases of MS. Further research and clinical trials will be necessary to fully explore their efficacy in treating MS and addressing barriers to cognitive impairment.

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