

# Bruton's Tyrosine Kinase Inhibitors in Multiple Sclerosis

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B cells play a central role in the pathogenesis of multiple sclerosis (MS), as demonstrated through the success of various B cell-depleting monoclonal antibodies. Bruton's tyrosine kinase (BTK) is a critical molecule in intracellular signaling from the receptor of B cells and receptors expressed in the cells of the innate immune system. BTK inhibitors may be a non-cell-depleting alternative to B cell modulation.

Keywords: Bruton's tyrosine kinase ; multiple sclerosis ; B cells ; BTK inhibitors

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## 1. Introduction

Multiple sclerosis (MS) has classically been considered an autoimmune disease of the central nervous system (CNS) with a degenerative component that becomes increasingly more evident as the disease progresses. Both the adaptive and the innate arms of the immune system are involved in the pathogenesis of MS. Even though immunoglobulin abnormalities found in the cerebrospinal fluid (CSF) are the most conspicuous immunological finding, it was still believed that anomalies of the humoral response did not have the same pathogenetic relevance as those of the cellular response. Knowledge derived from experimental autoimmune encephalomyelitis (EAE) has also contributed to the view of MS as a T-cell disease. Strong support against this view was provided by the results of a phase II clinical trial with rituximab, a monoclonal antibody depleting CD20+ B cells in patients with relapsing-remitting MS who showed a rapid and profound response in clinical and magnetic resonance imaging (MRI) parameters <sup>[1]</sup>. However, another anti B-cell trial using a fusion protein, atacicept—which binds to the cytokines, BlyS and APRIL, and is involved in B-cell maturation, differentiation, and survival—had to be prematurely terminated due to disease reactivation. This failure revealed the complexity of the pathogenic role of B cells in MS <sup>[2]</sup>. Two phase III trials with ocrelizumab and ofatumumab further confirmed the beneficial effect of B cell depletion with anti-CD20+ monoclonal antibodies <sup>[3][4]</sup>.

B cells are potent APCs that can drive T-cell mediated autoimmunity <sup>[5]</sup>. In EAE, they have a critical pathogenetic role, dependent on MHC II, and independent of their humoral response <sup>[6]</sup>. Memory B cells from MS patients elicited CD4+ T cell proliferation in response to myelin basic protein (MBP) and myelin-oligodendrocyte glycoprotein (MOG), a finding not reproduced with memory B cells from healthy donors <sup>[7]</sup>. B cells produce pro-inflammatory cytokines, such as lymphotoxin alpha, IL6, IL2, IL17, and tumor necrosis factor-alpha (TNF- $\alpha$ ) <sup>[8]</sup>. B cells from MS patients secrete more IL6 than healthy controls <sup>[9]</sup> and abnormally secrete TNF- $\alpha$  and lymphotoxin when activated with interferon- $\gamma$  or the pathogen-associated CPG-DNA <sup>[10]</sup>. On the other hand, B cells can act as regulators in autoimmunity by different anti-inflammatory cytokines, mostly IL10 <sup>[11]</sup>. Mice with IL10-deficient B cells develop a more severe EAE <sup>[12]</sup>. In MS patients, B cells produce a decreased average secretion of IL10 <sup>[13]</sup>. Ectopic follicle-like aggregates containing B cell and plasma cells may appear in meninges from patients with secondary progressive MS <sup>[14]</sup>; however, early MS <sup>[15]</sup> can also be associated with cortical demyelination <sup>[15][16]</sup>. In the CNS of progressive MS, antigen-experienced B cell clones obtained from meninges were related to clones that were isolated from inflammatory infiltrates, normal-appearing white matter, and CSF <sup>[17]</sup>. Importantly, the immunological abnormalities of B cells can be detected on both sides of the BBB—as demonstrated by the sequencing of IgG heavy chain variable region genes (IgG-VH) of samples of CSF and blood processed in parallel—indicating the exchange of these cells across the BBB <sup>[18]</sup>.

Currently, B cells are considered fundamental players in the pathogenesis of MS <sup>[19]</sup>.

Based on the fundamental role of B cells in MS pathogenesis, and considering the profound therapeutic impact of anti-CD20+ monoclonal antibodies, other anti-B cell alternatives have been explored to circumvent the problems associated with chronic B-cell depletion, such as humoral deficiency <sup>[20]</sup>. Bruton's tyrosine kinase (BTK) has emerged in recent



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For B cell malignancies, BTK inhibition by small molecules represents a major therapeutic advance. The enthusiasm for these types of drugs has expanded toward the field of autoimmune diseases with B cell-dependent pathogenesis. Quesenberry, R.; et al. Phase I Clinical Trial of PRN2246 (SAR441268), a Covalent BTK Inhibitor Demonstrates Experience with BTKi has developed with experimental models of several human autoimmune diseases, but clinical safety, CNS exposure and therapeutic levels of BTK occupancy. *Mult. Scler. J.* 2019, 5, 52.

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Since the introduction of ibrutinib, safety has been an essential concern for developing new BTKi. In theory, non-covalent reversible inhibitors would be more appropriate for autoimmune disorders, at the cost of lower efficacy. Published evidence from a phase II trial with the irreversible inhibitor, ibrutinib, suggested that it has an acceptable safety profile. Only the long-term exposure of MS patients to both types of BTKis in phase III clinical trials will provide a larger perspective concerning safety and tolerance.

In animal models of autoimmune diseases, including MS, results with different BTKis have raised expectations, and time will show whether the efficacy of those models translates to human diseases [34]. In EAE, experience with evobrutinib revealed the drug's central mechanism of action, inhibiting the activation of pathogenic T cells, a mechanism shared by anti CD20+ monoclonal antibodies [29]. It is inevitable to comment on the differential effects of those antibodies versus BTKi in MS. A phase II trial with rituximab showed an almost immediate and robust cancellation of CNS inflammation, detected as soon as four weeks after the first dose, with a marked effect on relapses [1]; in contrast, only one dose of evobrutinib achieved a significant reduction on MRI lesions from weeks 12 to 24, with no effect on secondary outcomes [35]. Compared to evobrutinib, and even though direct comparisons are not feasible, evidence indicates that the anti-CD20+ monoclonal antibodies exert a level of disease control that is not reached by evobrutinib. However, regarding efficacy against MS, the available information is preliminary, making it difficult to draw conclusions on BTKi. We will only know the real impact of those compounds on MS after the completion of the currently ongoing phase III clinical trials. BTKi offers a series of good points for long-term therapy: ease of administration and access to the CNS for the effective control of inflammation and the possibility of utilization in conjunction with anti-CD20+ antibodies, not as combined therapy, as is used in B cell malignancies—in which different clinical protocols associate BTKi with rituximab (or other anti-CD20+ antibodies) [36]—but in sequence, as suggested by Torke et al. [29]. Sequential use after B cell depletion with these antibodies would have the advantage of rapid inflammatory control, followed by drugs that inactivate B cells without significant effects on immunoglobulin levels.

## 4. Conclusions

Over the last three decades, immune therapy for MS has passed important milestones, effectively controlling clinical and MRI activity, even in patients with significantly active disease, slowing the accumulation of disability and delaying entry into the secondary progressive phase [37][38]. Despite modest advances with SPMS or PPMS, progression has been a stumbling block for therapy. Progression in MS is complex and is thought to depend on different factors, some of which are not well understood. Persistent inflammation within the CNS stands out as one of the candidate factors. Inflammation accompanies myelin damage alongside the evolution of the disease; the composition of the inflammatory infiltrate includes CD8+ T lymphocytes, B cells, activated microglia, and macrophages [39]. In chronic stages, BBB permeability is

restored, preventing the entry of therapeutic agents. Compartmentalized or “trapped” inflammation <sup>[40]</sup> in the CNS has become an important challenge for therapy, and it may be a major contributor to myelin and axonal damage. Additionally, the presence of ectopic B cell follicle-like structures in the meninges are related not only to cortical damage <sup>[15][16]</sup> but also to spinal cord pathology <sup>[41]</sup>.

For MS, the availability of a family of new drugs that can reach therapeutic concentrations inside the CNS, counteract the inflammation driven by B cells, and modulate the critical players in innate immunity, such as macrophages and microglia, is a therapeutic promise, because other disease-modifying drugs do not fulfill those aims. If these inhibitors effectively control persistent CNS inflammation, this could represent a great step toward the prevention of MS progression. We are currently in the preliminary—albeit exciting—stage of development, with many ongoing clinical trials hoping that the promise of BTKi will turn into reality. Intense clinical research will follow in the coming years.