2024 Volume 9, Issue 2
Advances in Precision Medicine
ISSN: 2424-9106 (Online)
ISSN: 2424-8592 (Print)

The Role of B Lymphocyte Stimulator/A Proliferation-Inducing Ligand in Neuroimmune Diseases

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Abstract:

B lymphocyte stimulator (BLyS) and a proliferation-inducing ligand (APRIL), both belonging to the tumor necrosis factor superfamily, exhibit significant homology. Functioning as lymphocyte co-stimulators, BLyS and APRIL regulate various biological processes, including cell differentiation, proliferation, survival, and importantly, immune functions of B and T cells. These molecules play a pivotal role in the pathogenesis and progression of neuroimmune diseases, such as neuromyelitis optica spectrum disorders, multiple sclerosis, and myasthenia gravis. This paper aims to enhance the understanding of BLyS/APRIL and their involvement in neuroimmune diseases.

Keywords:

B-cell activating factor
A proliferation-inducing ligand
Neuroimmune diseases
Pathogenesis

Online publication: December 27, 2024

1. Introduction

B lymphocyte stimulator (BLyS), also known as B-cell activating factor (BAFF), zTNF4, THANK, TALL-1, and TNFSF-13b, and a proliferation-inducing ligand (APRIL), also referred to as TALL-2, TRDL-1, and TNFSF-13a, are both members of the tumor necrosis factor (TNF) superfamily and are produced by a range of innate cells [1,2]. BLyS and APRIL share strong homology, with 30% of their sequences being common [2]. BLyS can bind to three receptors, including the B-cell maturation antigen (BCMA) and the transmembrane activator and calcium-modulating and cyclophilin ligand interactor (TACI). These two receptors, BCMA and TACI, can also bind to APRIL. These receptors are primarily expressed on the surface of most lymphocytes. Consequently, the binding of BLyS/APRIL to their respective receptors plays a crucial role in regulating the immune functions of B and T lymphocytes [3-6].

BLyS/APRIL are key factors regulating B lymphocyte function, particularly playing a significant role in autoimmune diseases such as systemic lupus erythematosus (SLE) and hematological malignancies [7]. However, the role of BLyS/APRIL in neuroimmune diseases has not been systematically summarized. Therefore, we searched PubMed for articles published from 2013 to 2023 on the role of BLyS/APRIL in

neuroimmune diseases using search terms such as “BLyS,” “APRIL,” “BAFF,” “neuroimmune diseases,” and “treatment.” This review aims to enhance understanding of BLyS/APRIL and their role in neuroimmune diseases.

2. Overview of BLyS/APRIL and their receptors

2.1. Overview of BLyS/APRIL

BLyS, a member of the TNF superfamily, is a type II transmembrane protein consisting of 285 amino acids. It is primarily expressed in myeloid cells, including monocytes, macrophages, dendritic cells, and activated neutrophils, and to a lesser extent in mesenchymal cells and T cells [8,9]. BLyS is a crucial regulator in processes such as B cell maturation, differentiation, and immune type conversion [10].

APRIL, also a member of the TNF superfamily, is closely related to BLyS. It can be secreted by monocytes, macrophages, dendritic cells, B cells, activated T cells, and certain tumor cells. APRIL is expressed at low levels in lymphocytes and at high levels in some tumor cells [11]. It promotes the activation of mature B cells and plasma cells, the differentiation of mature B cells into plasmablasts, and the class switching of B cell IgA and IgG. APRIL is also an important cytokine involved in B cell antigen presentation and plasma cell survival [12-16].

BLyS and APRIL are essential for maintaining B cell homeostasis and humoral immunity. BLyS regulates the differentiation and maturation of immature B cells, while APRIL regulates plasma cell function and survival. Additionally, BLyS and APRIL can participate in T cell activation under certain conditions. Both play significant roles in autoimmune diseases [17].

2.2. Overview of BLyS/APRIL receptors

Structurally similar, BLyS exists in soluble trimeric and membrane-bound forms, while APRIL exists in soluble trimeric, heparan sulfate proteoglycan (HSPG)-bound, and membrane-bound forms [17]. BLyS can bind to three receptors: BAFF receptor (BAFF-R, also known as BR3 or TNF receptor superfamily member 13C) [18], TACI (also known as TNF receptor superfamily member 13B) [19], and BCMA (also known as TNF receptor superfamily member 17) [20]. BLyS can bind to all three receptors, while APRIL can bind to TACI and BCMA [21]. BLyS and APRIL are widely expressed in various cells, but their receptors are primarily expressed in specific immune cells. All three receptors are expressed in B cells, with varying expression levels among different B cell subpopulations [22-24]. BAFF-R is mainly expressed in transitional and mature B cells, promoting the transition of T1B cells to T2B cells and the generation of mature B cells. It is involved in regulating B cell development and maturation. TACI is primarily expressed on the surface of mature B cells and plasma cells, participating in antibody class switching (IgM-G, A), mature B cell survival, and differentiation into plasma cells. Inhibiting the TACI pathway can reduce plasma cell production and IgG/IgA formation. BCMA is mainly expressed in plasma cells, maintaining their survival and antibody secretion [25,26]. These ligands and receptors interact to promote B cell differentiation, proliferation, survival, and effector functions.

Additionally, the receptors for BLyS and APRIL are expressed at low levels in T cells. For instance, BAFF-R expression is detectable in unactivated $CD4^+$ and $CD8^+$ T lymphocytes and regulatory T cells (Tregs) [27], with significantly increased expression upon T cell receptor activation. BCMA is also expressed in T cell subpopulations, albeit at much lower levels than BAFF-R [28], and TACI is expressed in activated T cells [29]. Therefore, the binding of BLyS and APRIL to their receptors can partially affect T cell function.

Beyond T and B lymphocytes, BAFF-R is also expressed in monocytes and dendritic cells [30,31], TACI is expressed in myeloid progenitor cells and macrophages [23,30], and BCMA is partially expressed in monocytes, natural killer cells, and plasmacytoid dendritic cells [5,32-34]. Thus, while primarily affecting adaptive immunity, BLyS/APRIL may also partially influence innate immune functions.

3. Role of BLyS/APRIL in the immune system

As lymphocyte co-stimulatory factors, BLyS/APRIL regulate various biological functions, particularly exerting a strong effect on B lymphocytes. Binding to receptors on the surface of effector cells, they transmit signals

intracellularly, regulating cell differentiation, proliferation, survival, and effector functions [35]. Additionally, studies have revealed that they partially affect T lymphocyte and myeloid cell functions, playing a crucial role in the regulation of autoimmune homeostasis.

3.1. Effects on B cells

3.1.1. Effects of BLyS/APRIL on B cells

BLyS has a strong chemotactic effect on B cells and plays a critical role in stimulating their differentiation and proliferation. Studies have shown that BLyS mRNA is expressed in all B-cell subtypes in the bone marrow, spleen, and peritoneal cavity of BALB/c mice, whereas APRIL is primarily expressed during the early stages of B-cell development in the bone marrow and in the peritoneal B1 cell subtype. *In vitro*, B1 and B2 cells stimulated with lipopolysaccharide can differentiate into plasma cells, expressing BLyS and APRIL intracellularly, with enhanced membrane expression of BLyS [2]. Overexpression of BLyS inhibits B cell receptor (BCR)-induced B cell apoptosis. In transgenic mice overexpressing BLyS, there is a significant increase in the number of mature B cells in peripheral circulation and lymphoid organs, accompanied by lymphoid organ enlargement and hyperglobulinemia. Both BLyS and APRIL stimulate B cell proliferation *in vitro* and *in vivo* [3,36].

BLyS induces the production of the anti-inflammatory cytokine IL-35 in regulatory B cells (Bregs) through the classical nuclear factor kappa-B pathway [37]. It also promotes B cell proliferation and survival by inhibiting autophagy and activating the Akt/mTOR signaling pathway in B cells [38]. Both BLyS and APRIL induce the phosphorylation of transcription factors AP-1 and STAT3 in marginal zone B cells and $CD5^+$ B1 cells, leading to the differentiation and expansion of IL-10-producing Bregs under inflammatory conditions [39-41]. APRIL primarily regulates the later stages of B cell differentiation and is crucial for the survival of long-lived plasma cells in the bone marrow [42], although APRIL deficiency does not affect B cell maturation in mice [43].

3.1.2. Effects of BLyS/APRIL and their receptors on B cells

In the bone marrow, progenitor B cells differentiate into immature B cells, which then exit the bone marrow and differentiate into mature B cells in the periphery [44]. BAFF-R is highly expressed in immature B cells, and its synergistic effect with BCR signaling promotes the transition of immature B cells to mature B cells [45]. Despite some conflicting results, BCR and BLyS-BAFF-R are also critical for memory B cells [46]. The survival of peripheral B cells depends on BAFF-R-mediated modification of nuclear chromatin, upregulation of nuclear factor kappa-B target gene promoters, and survival genes [47]. BLyS influences IL-10-producing B cells through BLyS receptors during immune responses [48]. Studies have found that the absence of BLyS or BAFF-R impairs B cell differentiation in mice [18,49]. Thus, the binding of BLyS to BAFF-R is essential for the development of mature B cells.

During the differentiation of B cells into plasma cells, BAFF-R expression is downregulated, while BCMA and TACI expression are upregulated [50]. TACI is crucial for specific antigen responses of T cell-independent B cells and regulates B cell and immunoglobulin isotype switching. TACI receptors are located on $CD27^+$ memory B cells and plasma cells, so they have no significant effect on early B cell development stages [51]. However, they are essential for the differentiation and survival of CD40, lipopolysaccharide, and immune-induced plasmablasts and plasma cells [13,52]. BCMA mediates the homeostatic survival of plasma cells and is crucial for the survival of long-lived plasma cells. However, it has a weak role in B cell development and differentiation, and mice with BCMA deficiency have normal B cell counts [49,53]. The precise regulation of these receptors effectively targets B cell differentiation.

3.2. Effects on T cells

3.2.1. Effects of BLyS/APRIL on T cells

T cells are another source of BLyS and APRIL, and high expression of BLyS and APRIL can be induced by stimulating helper T cells Th1 and Th2 *in vitro* [54]. However, BLyS and APRIL do not directly stimulate T cells. Instead, they act as co-stimulatory factors that activate naive T cells or memory $CD4^+$ and $CD8^+$ T cells [55,56]. Overexpression of APRIL promotes T cell activation, and its role in T cell-related immune responses is associated with increased serum IgM levels [54].

3.2.2. Effects of BLyS/APRIL and their receptors on T cells

Studies have found that treatment with TACI-Ig in arthritic mice reduces BLyS/APRIL expression levels, inhibits TACI and BCMA, decreases the expression of proinflammatory Th1 and Th17 cytokines, and increases the expression of anti-inflammatory Tregs and Th2, demonstrating its potential effects on T cells [1]. The BLyS-BAFF-R signal promotes T cell survival and proliferation by activating the PI3K-Akt pathway, activating cytokines such as IL-2, interferon-gamma, IL-4, and transforming growth factor-beta, and facilitating the activation and expansion of $CD4^+$ T cell subsets and Tregs [55,57].

Research has shown that T cells from BAFF-R mutant A/WySnJ mice do not respond to BLyS co-stimulation. BAFF-R is expressed on activated/memory T cell subsets with no significant expression of TACI and BCMA [58]. Neutralization of BAFF-R promotes the activation and cytolytic function of $CD4^+$ and $CD8^+$ T cells [28]. BAFF-R is the primary mediator of BLyS-dependent co-stimulatory responses in peripheral B and T cells [58].

3.3. Effects on natural killer cells

Natural killer cells also express BLyS, but at lower levels compared to other immune cells [59]. Under IL-2 stimulation, BLyS expression levels in natural killer cells are significantly higher than in monocytes [60]. There is limited research on the effects of BLyS/APRIL on other immune cells. However, studies have found that the BLyS-BAFF-R signal is essential for maintaining the homeostasis and maturation of splenic natural killer cells [61]. The effect of BLyS on natural killer cells is indirect, possibly mediated through B cell-induced stromal cell development and the accumulation of follicular dendritic cells in the spleen, as well as the production of the natural killer cell survival factor IL-15 by these cells. Other studies have demonstrated that BLyS enhances the cytotoxic effects of natural killer cells by upregulating IL-2 and interferon-gamma production by $CD4^+$ T cells [62].

4. The role of the BLyS/APRIL axis in neuroimmune diseases

Multiple studies have found that BLyS/APRIL plays a significant role in the occurrence and development of systemic autoimmune diseases such as SLE and rheumatoid arthritis (RA) [2,63-65]. Its role in neuroimmunological diseases is also receiving increasing attention. The receptors for BLyS/APRIL are primarily expressed on the surface of most lymphocytes. When BLyS/APRIL binds to its receptors, it promotes the maturation and differentiation of B cells and regulates T cell immune responses through autoantigen presentation [66,67]. Imbalances in BLyS/APRIL are associated with various inflammatory responses. Overexpression of BLyS/APRIL can lead to abnormal proliferation and activation of B cells, promoting differentiation into plasma cells and secreting large amounts of antibodies, resulting in abnormalities in autoimmune homeostasis and contributing to the development of autoimmune diseases [36]. Elevated levels of BLyS and APRIL are observed in many patients with autoimmune diseases, such as SLE, multiple sclerosis, neuromyelitis optica spectrum disorders (NMOSD), etc. [25,68].

4.1. Multiple sclerosis

Multiple sclerosis (MS) is a neuroimmune disease primarily mediated by T and B lymphocytes. Studies have found that levels of BLyS and APRIL in the cerebrospinal fluid (CSF) of MS patients increase during acute relapses [68]. High levels of BLyS and APRIL in the CSF of MS patients have been associated with characteristic imaging changes of MS [69]. Untreated MS patients have higher blood levels of BLyS and APRIL compared to healthy controls. Treatment with ocrelizumab, a CD20 monoclonal antibody, leads to a significant increase in blood BLyS levels at both 6 and 12 months, while blood APRIL levels decrease at 12 months. Additionally, an increased risk of infection after ocrelizumab treatment is associated with elevated blood BLyS levels [70]. However, some studies have reported no significant increase in blood BLyS levels in untreated MS patients compared to normal controls, but an increase after treatment with beta-interferon [71,72]. This may promote the generation of anti-inflammatory IL-10 by transitional B cells, rather than promoting the production of pro-inflammatory class-switched memory B cells [73]. In BLyS-Tg mice, overexpression of BLyS has been found to have a protective effect on experimental autoimmune encephalomyelitis (EAE) [74]. Through a

TACI-dependent mechanism, BLyS overexpression significantly increases the accumulation of IgA^+ plasma cells/plasmablasts and subsequent IL-10 release in the gut. These anti-inflammatory factors inhibit the production of pathogenic gamma interferon and IL-17 in the brain, leading to improved EAE. Thus, BLyS/APRIL maintains the inflammatory balance of B cells, including both pro-inflammatory (antibody and inflammatory cytokine production) and anti-inflammatory (IL-10 production) responses. Disruption of this balance may contribute to the exacerbation of MS. Further research exploring ways to promote BLyS/APRIL-mediated anti-inflammatory responses in B cells may offer hope for new therapeutic approaches for MS.

4.2. Neuromyelitis optica spectrum disorders

Neuromyelitis optica spectrum disorder is an autoimmune disease of the central nervous system primarily mediated by antibodies against aquaporin 4 (AQP4). Studies have found that levels of BLyS and APRIL in the CSF of NMOSD patients increase during acute episodes and are correlated with disease severity [68,75,76]. Treatment with immunosuppressive agents leads to a decrease in serum BLyS levels [77]. Postmortem pathological findings from one NMOSD patient suggest that APRIL-producing cells are closely associated with plasma cells in the meninges, indicating a potential role for targeting APRIL in plasma cells of the central nervous system. Additionally, APRIL targets activated astrocytes, suggesting its possible role in NMOSD lesions [78]. Therefore, BLyS/APRIL plays a potential role in NMOSD.

4.3. Myasthenia gravis

The main pathogenesis of myasthenia gravis (MG) is the production of autoantibodies such as acetylcholine receptor antibodies (AchR-Ab), which lead to neuromuscular junction transmission disorders and cause muscle weakness. BLyS is believed to have an impact on the development of MG patients. The serum BLyS level in AchR-Ab-positive MG patients is significantly higher than that in healthy controls, and it is positively correlated with AchR-Ab titers [79]. The blood BLyS titer in muscle-specific tyrosine kinase antibody (MuSK-Ab)-positive MG patients is correlated with disease severity [80]. After glucocorticoid therapy, the serum BLyS level in MG patients decreases, suggesting that the inhibitory effect of hormones on BLyS may be a potential mechanism for effective treatment [81]. Some researchers have found that the rs2893321 gene polymorphism in BLyS may be associated with the susceptibility to MG in the Chinese Han population [82]. In addition, a comparison of serum levels between 43 AchR-Ab-positive MG patients and 25 healthy controls showed that the levels of APRIL, IL-19, IL-20, IL-28A, and IL-35 in the serum of MG patients were significantly increased, and APRIL and IL-20 were elevated in patients with late-onset MG [83]. Many research results suggest that elevated levels of BLyS and APRIL in MG patients are associated with disease characteristics [83,84]. These findings suggest that BLyS/APRIL may affect the occurrence and development of MG.

5. Progress in clinical research on targeting BLyS/APRIL for the treatment of neuroimmunological diseases

Targeted B-cell therapy is a very promising treatment strategy in the field of neuroimmunological diseases, with therapeutic drugs including rituximab, belimumab, and telitacicept [85]. Fusion protein drugs targeting BLyS/APRIL can not only achieve direct inhibition of B cells, inhibit the transformation of immature B cells into mature B cells, and inhibit the transformation of mature B cells into plasma cells, but also promote the apoptosis of plasma cells. However, it does not completely eliminate B cells and plasma cells [86]. Therefore, drugs targeting BLyS/APRIL as therapeutic targets are receiving increasing attention in neuroimmunological diseases [87]. Currently, there are drugs targeting BlyS and drugs targeting both BLyS and APRIL.

5.1. Belimumab

Belimumab is a recombinant fully human monoclonal IgG1 antibody that can specifically bind to and inhibit BLyS activity. It has been approved for the treatment of SLE and lupus nephritis. Additionally, Phase II/III studies are currently underway for its application in refractory idiopathic myositis and other diseases (NCT02347891). For neuroimmunological diseases, there are studies on the use of belimumab in MG. The results of a Phase II clinical study of belimumab in the treatment of MG showed no

significant difference in the quantitative MG score at 24 weeks compared to the control [88]. The subjects included in the study had mild disease severity, the selected score was not sensitive to minor symptom changes, and anti-MuSK-Ab-positive MG patients who were effective with B-cell therapy were not included, which may have affected the results [89,90].

5.2. Tabalumab and blisibimod

Tabalumab is a fully human monoclonal antibody targeting both membrane-bound and soluble BLyS. Clinical studies were conducted in patients with RA and SLE [91], but further research was not pursued due to failure to achieve efficacy endpoints. Blisibimod is also an antibody targeting BlyS. It underwent Phase III clinical studies in SLE patients but similarly failed to achieve efficacy endpoints and increased disease activity in some seropositive SLE patients, ultimately ending in failure [2,24]. These two drugs have not yet been studied in neuroimmunological diseases. The possible reason for their unsatisfactory efficacy is that BLyS is not the only factor regulating B-cell function, and APRIL also plays an important role.

5.3. Atacicept

Atacicept is an early recombinant fusion protein of human TACI and IgG. It has undergone Phase III clinical studies in SLE patients (NCT00624338), Phase II clinical studies in RA patients, and Phase I clinical studies in hematological malignancies such as chronic lymphocytic leukemia, multiple myeloma, and non-Hodgkin's lymphoma [92]. In neuroimmunological diseases, a double-blind randomized controlled clinical study of atacicept in the treatment of MS showed that atacicept increased MS disease activity, leading to early termination of the study [93]. Another Phase II clinical study of atacicept in 17 patients with isolated syndrome presenting with unilateral optic neuritis as the initial symptom found that more patients in the atacicept treatment group developed MS compared to the placebo control group (35.3% vs. 17.6%) [94].

5.4. Telitacicept

Telitacicept is a novel fully human recombinant fusion protein consisting of the extracellular domain of human TACI fused with the crystallizable fragment (Fc) domain of human IgG1 through recombinant DNA technology. Bioinformatic optimization of the fusion protein structure has overcome the issue of easy degradation of natural TACI protein, resulting in a more stable structure with stronger biological activity and high protein expression. Compared to atacicept, the integrated TACI fragment in telitacicept is longer [17]. Soluble TACI has been observed to neutralize both BLyS and APRIL in a mouse model expressing soluble TACI [95,96]. Utilizing the principle that TACI can bind to both BLyS and APRIL simultaneously, telitacicept can block the abnormal B-cell maturation, differentiation, and antibody production mediated by BLyS, APRIL, and their three receptors. It regulates the activation of B and T cells, thereby helping to control the occurrence and development of diseases [50,97]. Telitacicept has demonstrated therapeutic effects on autoimmune diseases such as SLE, significantly inhibiting B-cells, proinflammatory cytokines, and immunoglobulin levels [98]. It was approved for the treatment of SLE in China in 2021 [17,99]. A single-center, single-arm, open-label clinical study conducted by our team on plasma exchange combined with telitacicept for the treatment of NMOSD found that compared to the previous year before enrollment, patients had a prolonged time interval between the first recurrence and a reduced number of recurrences. The Expanded Disability Status Scale (EDSS) score improved from 3.5 (2.5~4.5) to 3 (1~4), and no serious adverse events occurred. These findings suggest that telitacicept's dual-target inhibition of BLyS and APRIL likely has a beneficial effect on reducing recurrences and improving disability in NMOSD patients, with acceptable drug safety [100,101]. However, further multicenter, randomized controlled studies are still needed to confirm these results. Currently, a Phase III clinical study (NCT03330418) evaluating telitacicept for the treatment of NMOSD is ongoing in China, with the primary endpoint being time to recurrence and secondary endpoints including changes in EDSS score and Hauser Ambulation Index. A Phase II clinical study (NCT04625153) for MS is also in progress. In 2022, a Phase II clinical study (NCT04302103) of telitacicept for the treatment of generalized MG was completed and yielded positive results, demonstrating significant improvement in patients' conditions with good safety and

efficacy. Telitacicept was included in the breakthrough therapy category by the China National Medical Products Administration's Center for Drug Evaluation in November 2022. Currently, a Phase III clinical study (NCT05737160) for MG is ongoing.

As shown in **Table 1**, drugs targeting BLyS/APRIL have shown certain potential in the treatment of neuroimmunological diseases. However, some controversies remain, and further high-level evidence studies are still needed.

6. Conclusion

In summary, BLyS/APRIL are important factors in the immune system, particularly in regulating B cells and humoral immunity. We have summarized the role of BLyS/APRIL in the immune system, especially in neuroimmunological diseases. Targeting the inhibition of BLyS/APRIL may be a promising therapeutic approach based on their role in the occurrence and development of neuroimmunological diseases, but further research is still needed to confirm this.

Table 1. Drugs targeting B lymphocyte stimulator/a proliferation-inducing ligand

Medications	Types	Therapeutic targets	Applications in other diseases	Applications in neuroimmune diseases
Belimumab	Fully humanized recombinant monoclonal IgG1 antibody	Soluble BLyS	Approved treatments: Systemic Lupus Erythematosus (SLE), Lupus Nephritis (LN) Clinical research: Refractory idiopathic myositis, Rheumatoid Arthritis (RA), Sjögren's Syndrome	MG Phase II clinical study: After 24 weeks of treatment, the QMG score showed no significant difference compared to the placebo control.
Tabalumab	Monoclonal antibody	Soluble and membrane-bound BLyS	Phase III clinical trials: SLE, RA	None
Blisibimod	Peptide and antibody	BLyS	Phase III clinical trials: SLE	None
Atacicept	Recombinant fusion protein of human TACI receptor and IgG, earlier than Telitacicept	BLyS and APRIL	Phase II/III clinical trials: SLE, LN, RA Phase I clinical trials: Chronic Lymphocytic Leukemia (CLL), Multiple Myeloma (MM), Non-Hodgkin Lymphoma (NHL), Waldenström Macroglobulinemia (WM)	MS Double-Blind Randomized Controlled Phase II Clinical Study: An increase in disease activity was observed. Optic Neuritis Phase II Clinical Study: The treatment group showed a higher likelihood of progression to MS.
Telitacicept	Fully humanized recombinant fusion protein of TACI and IgG1; incorporates a longer TACI fragment compared to Atacicept	BLyS and APRIL	Approved for treating SLE; Clinical research: IgA Nephropathy, RA, Sjögren's Syndrome	Generalized MG Phase II Clinical Study: By the 24th week, the QMG score significantly decreased, demonstrating high safety. NMOSD Single-Center Open-Label Clinical Study: Showed promising effects in reducing relapse rates, improving EDSS scores, and maintaining safety. Ongoing studies: MG and NMOSD Phase III Clinical Studies, MS Phase II Clinical Study

Disclosure statement

The authors declare no conflict of interest.

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