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Advances in B Cell Targeting for Treating Muscle-Specific Tyrosine Kinase-Associated Myasthenia Gravis

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Abstract: Myasthenia gravis (MG) is a typical autoimmune disease of the nervous system. It is characterized by skeletal muscle weakness and fatigue due to impaired neuromuscular junction transmission mediated by IgG autoantibodies. Muscle-specific receptor tyrosine kinase-associated MG (MuSK-MG), a rare and severe subtype of MG, is distinguished by the presence of anti-MuSK antibodies; it responds poorly to traditional therapies. Recent research on MuSK-MG treatment has focused on specific targeted therapies. Since B cells play a critical pathogenic role in producing autoantibodies and inflammatory mediators, they are often considered the preferred target for treating MuSK-MG. Currently, various B cell-targeted drugs have been developed to treat MuSK-MG; they have shown good therapeutic effects. This review explores the evolving landscape of B cell-targeted therapies in MuSK-MG, focusing on their mechanisms, efficacy, and safety, and the current limitations associated with their use. We discuss current B cell-targeted therapies aimed at depleting or modulating B cells via both direct and indirect approaches. Furthermore, we focus on novel and promising strategies such as Chimeric Autoantibody Receptor T cell therapy, which explicitly targets MuSK-specific B cells without compromising general humoral immunity. Finally, this review provides an outlook on the potential benefits and limitations of B cell-targeted therapy in developing new therapies for MuSK-MG. We conclude by discussing future research efforts needed to optimize these therapies, expand treatment options, and improve long-term outcomes in MuSK-MG management.

Keywords: MuSK-MG, B cell-targeted therapy, direct targeting, indirect targeting, MuSK-CAR-T, MuSK-CAAR-T

Introduction

Myasthenia gravis (MG) is a disease characterized by acquired neuromuscular junction (NMJ) transmission disorders mediated by autoantibodies, giving rise to skeletal muscle weakness and fatigue.[1] The disease can affect skeletal muscles throughout the body, significantly affecting the patient's daily life. Some patients may experience rapid disease progression within a short period, leading to a myasthenic crisis or even death.[2]

The global incidence of MG is approximately 0.3–2.8/100,000.[2] Acetylcholine receptor (AChR)-specific antibodies could be detected in most patients with MG, with approximately 5–8% having specific antibodies against muscle-specific receptor tyrosine kinases (MuSK) or Low-density lipoprotein receptor-related protein 4 (LRP4) in their serum.[3,4] AChR-Ab directly causes disease by cross-linking achRs, complement binding and activation, and by inducing AChR conformational changes or blocking acetylcholine binding.[5–7] MuSK-Ab carries out Fab arm exchange to bind to

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MuSK with functional monovalent, inhibit the dimerization and phosphorylation of MuSK, and affect the aggregation of downstream AChR.[7] LRP4-Ab binds to membrane proteins in vivo and blocks Agrin-LRP4 interaction, thereby also inhibiting AChR aggregation in the membrane.[8]

Due to various autoantibodies that trigger MG, clinical symptoms are highly heterogeneous. MuSK-MG often develops acutely and progresses rapidly within a few weeks. It is clinically more severe than other MG subtypes, with up to 80% of patients with MuSK-MG demonstrating bulbar muscle damage, including dysarthria, dysphagia, and difficulty chewing.[3,9,10] In addition, MuSK-MG patients have a higher risk of myasthenic crisis, occasional muscle atrophy, and relapse post-treatment.[3]

Most patients with MuSK-MG show limited or no response to anticholinesterase drug treatment, which may be harmful.[11] Furthermore, patients with MuSK-MG demonstrate poor responsiveness to intravenous immunoglobulin (IVIg), thymectomy, and complement blockade therapy.[12–14] The primary treatments include glucocorticoids, azathioprine, plasma exchange, rituximab (RTX) and FcRn-targeted drugs efgartigimod and rozanolixizumab, though corticosteroids and conventional immunosuppressive drugs may not adequately control long-term clinical symptoms and can induce side effects.[15–17] Steroids are the standard treatment, but approximately 15% of patients exhibit refractory disease to high-dose steroids. RTX, while effective, leads to general B cell depletion, reduction in total IgG level, and immunosuppression.[18–23] An ideal treatment selectively targeting MuSK-specific B cells while preserving normal B cells remains an unmet need in MuSK-MG therapy.

In recent years, immunotherapy targeting B cells has shown promising approaches for targeting MuSK-MG, with several therapies currently in development. This review discusses the latest advancements in B cell-targeted therapies for MuSK-MG, exploring their mechanisms of action, effectiveness, safety profiles, and limitations.

Role of B Cells in MuSK-MG

MuSK is an important neuromuscular junction protein crucial in forming and maintaining NMJs. It is a 100-kDa single-channel postsynaptic transmembrane receptor tyrosine kinase composed of three extracellular N-terminal immunoglobin (Ig)-like domains, a curled-like domain (Fz domain), and an intracellular kinase domain (Figure 1a).[24–26] Antigen epitope mapping studies indicate that MuSK-specific antibodies mainly bind to Ig1 and Ig2, as well as to the Fz domain in some

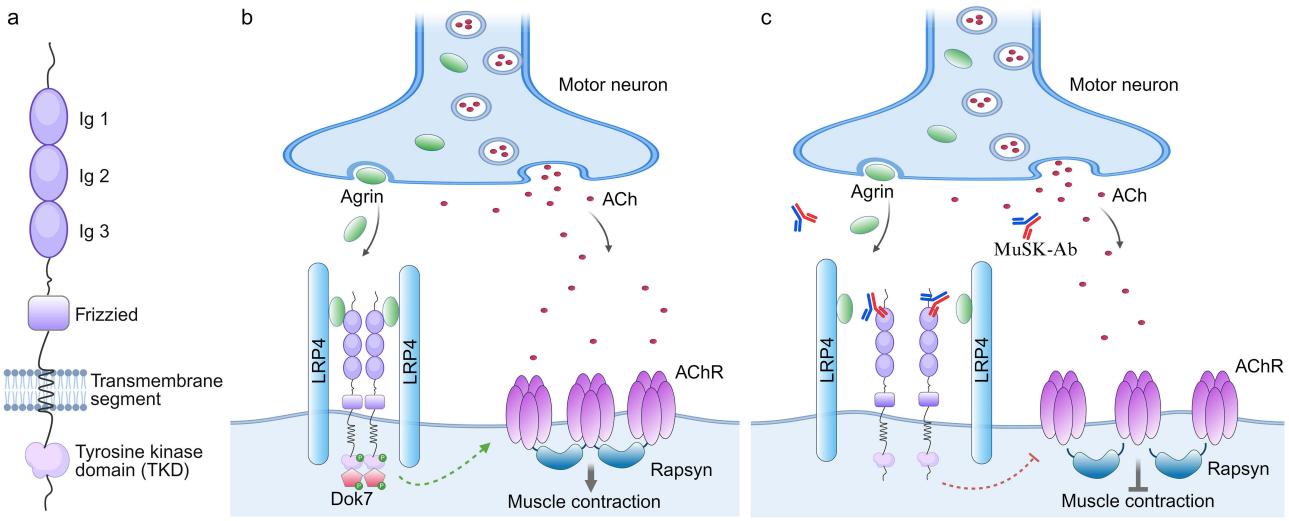

Figure 1 The structure of MuSK and the pathogenic mechanism of MuSK-Ab. (**a**) The structure of the MuSK protein is made up of an extracellular domain, an intracellular kinase, and a transmembrane domain. The extracellular domain contains three Ig-like domains (Ig1-3) and a Frizzled-like domain (Fz), which is a cysteine-rich domain (CRD). (**b**) LRP4 simultaneously engages both MuSK and Agrin, thereby facilitating their direct interaction. Subsequently, MuSK dimerizes and activates its intracellular kinase domain upon co-stimulation of LRP4 and Agrin. Activation of MuSK further recruits and stimulates Dok7 phosphorylation, which stimulates signal transduction of the downstream AChR cluster, promoting the aggregation of AChR. (**c**) When MuSK-specific antibodies are present in vivo, functional monovalent MuSK-Ab binds to the extracellular domain of MuSK, thereby blocking the interaction of MuSK with LRP4 and Agrin, inhibiting the dimerization and phosphorylation of MuSK, inhibiting the aggregation of downstream AChRs, and leading to neuromuscular excitation transmission disorders. (Image created with BioRender.com).

patients. However, the Ig1-like domain is the main target.[27–30] MuSK interacts with some proteins through the extracellular domain to enhance signal transduction in NMJs (Figure 1b).

B cells are essential for MuSK-MG pathogenesis, mainly by producing antibodies against MuSK, which leads to the destruction and dysfunction of NMJs. The secretion of MuSK-specific antibodies is primarily attributed to short-lived plasma cells, with the majority belonging to the IgG4 subclass.[31] Due to its unique hinge-region structural characteristics, IgG4 has functional monovalent and bispecific non-inflammatory properties and cannot participate in the cross-linking and internalization of target antigens.[14,32,33] Furthermore, most MuSK-IgG4 antibodies undergo Fab-arm exchange, producing bispecific antibodies that bind to the MuSK extracellular domain in a functional monovalent manner, thereby blocking low-density lipoprotein receptor-related protein 4 (LRP4)-MuSK interactions, preventing MuSK dimerization and phosphorylation, inhibiting AChR aggregation, and leading to neuromuscular excitation transmission disorders (Figure 1c).[11,27,34] Based on previous research, MuSK-specific antibodies contribute to the occurrence and development of MG by depleting MuSK molecules that are essential for muscle function. In recent years, most of the targeted therapies for MuSK-MG have focused on the depletion of B cells to reduce the levels of, or eliminate, MuSK-specific autoantibodies.

In addition, B cells can also play a role in antigen presentation during the autoimmune response. The B cell receptors (BCRs) directly bind to antigens and form antigen peptide-MHC molecule complexes with major histocompatibility complex (MHC) class II molecules, which are then presented to CD4+ T cells.[35] Moreover, B cells can express so-called co-stimulators, such as CD40, CD80, and CD86, which further lead to the activation of pro-inflammatory T cells and thus regulate the immune response.[36]

Since B cells play a critical pathogenic role in producing autoantibodies and inflammatory mediators, they are the preferred target for treating MuSK-MG. Targeting B cells and the antibodies they produce may be one of the important strategies for targeted therapy of MuSK-MG. B cell-targeted therapy includes direct targeting that consumes or inhibits different B cell subpopulations, indirect targeting that inhibits B cell maturation and differentiation-related cytokines or immune cells, chimeric antigen receptor-T cell therapy (CAR-T) and reverse targeting using chimeric autoantibody receptor (CAAR) T-cell therapy (Table 1).

Direct Targeting

Multiple CD antigens where located on the surface of B cells, which distinguish different B cell subsets and play crucial roles in their maturation, activation, differentiation, and survival. These CD molecules, whose expression can vary or become activated in pathological conditions, are valuable features on the cell surface for targeted B cell therapy. Direct targeted therapy achieves B cell depletion by specifically targeting surface-related antigens such as CD19 and CD40 (Figure 2).

CD20 (Rituximab)

RTX is a human-mouse chimeric monoclonal antibody (mAb) that can bind specifically to the transmembrane antigen CD20. RTX has gained widespread acceptance and application in the past few years.[37,38] CD20 is a glycoprotein expressed on pro-B cells, naive B cells, and all mature B cells, and is critical for B cell proliferation and differentiation.[39] RTX effectively depletes CD20-positive B cells, including mature B cells and memory B cells, and this reduction occurs through antibody-dependent cell-mediated cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC), and target cell apoptosis.[40,41] However, pro-B and plasma cells in the bone marrow and secondary lymphoid organs were largely unaffected.[42,43] This effect lasts approximately six months until circulating B cells are replenished.[38] Because AChR-Ab is mainly produced by long-lived plasma cells (which do not express CD20), RTX treatment is only effective in a subset of patients with AChR-Ab + MG.[44] In contrast, MuSK-Ab is mainly produced by short-lived plasma cells. Most patients with MuSK-MG respond well to RTX, achieving a remission rate approaching 100%. A 2017 blinded, multicenter, prospective evaluation by Professor Burns et al showed that 58% of patients with MuSK-MG treated with RTX met the primary clinical endpoint, compared to 16% of the control group.[18] In addition, a 2020 study by Bartoccioni et al revealed reduced titers of MuSK-IgG4 antibodies in patients and continued clinical improvement with RTX treatment.[21] Experience with rituximab in the treatment of myasthenia gravis in adolescents is limited to case reports and generally

Table 1 Major B Cell Targeting Drugs for MuSK-MG Treatment

Category	Drug	Target	Structure	Start Date	Study Type	Study Code	Study Status	Number of Participants	Results	Adverse Events
Direct Targeting	Rituximab	CD20	Human-mouse chimeric IgG1 κ mab	2016-10-16	Phase 3	NCT02950155	Completed	47 total	Positive	Infections, generalized skin itching, dyspnea, leukopenia and PML
	Inebilizumab	CD19	Humanized IgG1 κ mab	2020-08-30	Phase 3	NCT04524273	Ongoing	238 total (82 MuSK-Ab+)	Pending	Pending
	Mezagitamab	CD38	Fully human IgG1 mab	2020-01-14	Phase 2	NCT04159805	Completed (results not published)	36 total	Pending	Pending
	Iscalimab	CD40	Fully human Fc silent IgG1 mab	2015-09-29	Phase 2	NCT02565576	Completed (results not published)	44 total	The outcome measure of significant improvement in MG score was not achieved	No security issues currently
Indirect Targeting	Belimumab	BAFF	Fully human IgG1λ mab	2013-04	Phase 2	NCT01480596	Completed	40 total (2 MuSK-Ab+)	No significant effect	Infections, gastrointestinal side effects, nausea, influenza, and systemic reactions after infusion
	Telitacicept	BAFF and APRIL	Receptor-antibody fusion protein	2023-03-28	Phase 3	NCT05737160	Ongoing	100 total	Pending	Pending
	Bortezomib	26S proteasome	26S Proteasome inhibitors	2014-10	Phase 2	NCT02102594	Terminated	11 total (1 MuSK-Ab+)	Pending	Sensorimotor polyneuropathy
CAR-T	BCMA CAR-T	Plasma cells	CAR-T cells against BCMA	2020-09-22	Early Phase 1	NCT04561557	Ongoing	36 total (1 MuSK-Ab+)	Positive	Cytotoxicity, mitochondrial dysfunction
	BCMA rCAR-T	Plasma cells	rCAR-T cells against BCMA	2019-12-04	Phase 2	NCT04146051	Ongoing	30 total	Positive	Urticaria
	CD19 CAR-T	CD19+B cells	A fully human anti-CD19 CAR T-cell	2024-08-28	Phase 2	NCT06193889	Recruiting	–	Pending	Pending
CAAR-T	MuSK-CAAR-T	MuSK-specific B cells	Chimeric MuSK autoantibody receptor T cells	2022-11-23	Phase 1	NCT05451212	Recruiting	24 total	Pending	Pending

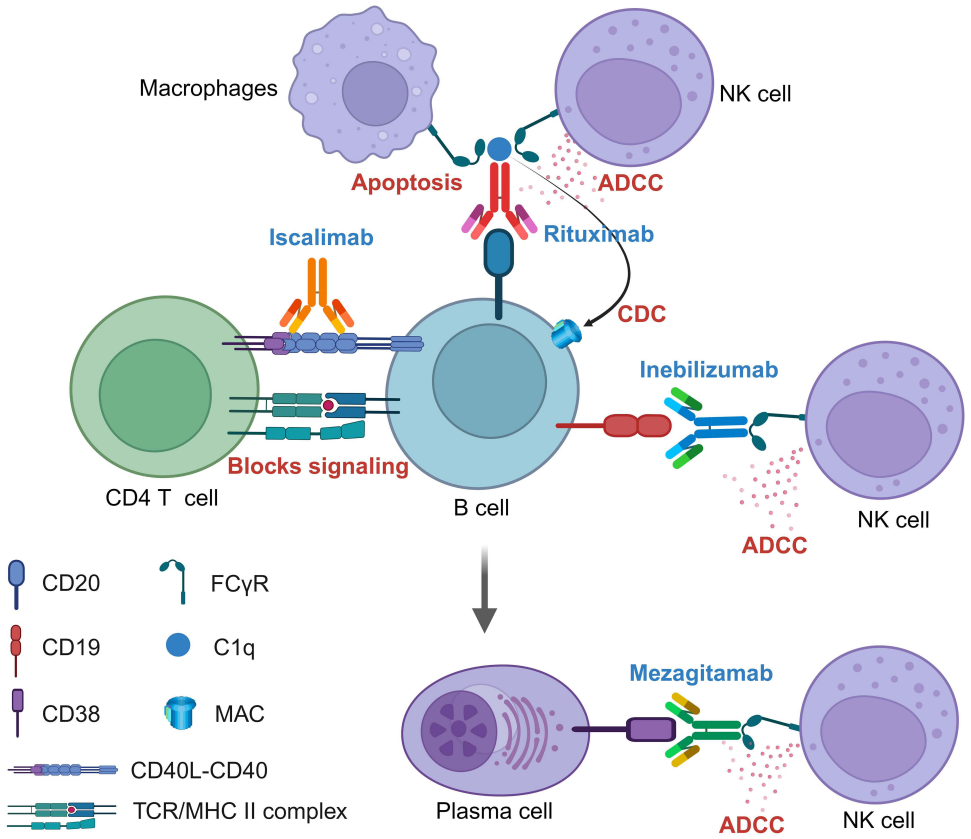

Figure 2 Mechanism of action of direct B cell-targeting drugs. The mechanism of action of rituximab includes antibody-dependent cell-mediated cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC), and target cell apoptosis. Inebilizumab consumes B cells expressing CD19 through ADCC. Mezagitamab kills B cells expressing CD38 through ADCC. Iscalimab can block the interaction of CD40-CD40L, thereby inhibiting the activation of CD40-positive cells. (Image created with BioRender.com).

works well in AChR-MG and MuSK-MG, as well as seronegative MG.[45,46] In a multicenter retrospective study of 27 pediatric MG patients treated with rituximab, all patients showed improvement and no adverse events occurred during treatment.[47] There is no clear consensus on the appropriate dosing regimen of rituximab in patients with MG, and although most studies have been conducted according to classical treatment guidelines (375 mg/m^2 / 4 weeks or 1 g / 2 biweekly dosing), in recent years, an increasing number of authors suggest that lower doses of rituximab can achieve the same clinical results with better safety and cost-effectiveness.[48–50] Despite the remarkable efficacy of RTX treatment in MuSK-MG, some patients usually relapse 1–3.5 years post-RTX treatment, and MuSK-specific B cells persist despite repeated RTX treatment. Minor patients do not respond to RTX treatment, which may be due to the existence of low expression of CD20-CD27+ B cells in peripheral blood of these patients, and the continuous production of anti-musk antibodies.[19–22] The broad depletion of CD20-expressing B cells by RTX poses infection and secondary immunodeficiency risks.[23] Studies have reported severe infection, generalized skin itching, dyspnea, leukopenia, or delayed progressive multifocal leukoencephalopathy (PML) after RTX treatment in some MG patients.[19,50–55]

CD19 (Inebilizumab)

Inebilizumab is a humanized, fucosylated IgG1 κ mAb that depletes CD19-positive B cells via the ADCC mechanism.[56,57] CD19 is distributed in early pro-B cells, most plasma cells in peripheral circulation, and approximately half of the plasma cells in the central immune organs.[21] This makes CD19 a potential target for depleting CD19-positive B cells, a strategy exemplified by inebilizumab. Approved in June 2020 for treating aquaporin-4 antibody-positive NMOSD, the safety and efficacy of inebilizumab are currently under evaluation for IgG4 disease.[56,58] Trials involving NMOSD patients revealed that inebilizumab is well tolerated, with mild to moderate side effects consistent with other B cell-depleting drugs.[56] Amgen initiated a Phase 3 study in August 2020 (NCT04524273), employing a randomized,

double-masked, multicenter, placebo-controlled design to evaluate the effectiveness and safety of inebilizumab in adult patients with MG (including 42 MuSK-MG). This study is anticipated to be completed in 2027 and will clarify the effectiveness and safety of inebilizumab.

CD38 (Mezagitamab)

Mezagitamab (TAK-079) is a fully human IgG1 mAb with a high affinity for cells that express CD38, such as plasma cells and natural killer (NK) cells. It induces cell death in B cells expressing CD38 through ADCC. CD38 is a transmembrane glycoprotein with extracellular enzyme activity expressed by leukocyte subsets, with the highest density on plasma cells and plasmablasts.[59] In 2020, Takeda Pharmaceuticals initiated a first-in-human Phase 1 trial (NCT02219256), which was randomized, double-masked, placebo-controlled, and single-dose, involving healthy adult subjects. It showed that TAK-079 was well tolerated, and subcutaneous injection resulted in sustained decreases in the plasmablast and NK cell counts.[60] A Phase 2 randomized, placebo-controlled study (NCT04159805) by Takeda Pharmaceuticals assessed the safety, tolerability, and efficacy of TAK-079 in patients with generalized MG (including MuSK-MG). This study was completed by July 2022, but the results have not yet been published. The efficacy and safety of TAK-079 specifically still require clarification.

CD40 (Iscalimab)

Iscalimab (CFZ533) is a fully human IgG1 mAb that lacks the Fc region, blocking the CD40 signaling pathway. This mechanism prevents the activation of CD40-positive cells but does not cause exhaustion. CD40 is expressed on lymphocytes and antigen-presenting cells, while the CD40 ligand (CD40L), also known as CD154, is mainly expressed by activated CD4+ T cells.[61,62] The interaction between CD40 and CD40L is essential for isotype conversion, germinal center formation, the development of memory B cells, and antibody production.[63] Novartis Pharmaceuticals conducted a multicenter, randomized, double-masked, placebo-controlled phase 2 clinical trial (NCT02565576) focusing on seropositive generalized MG (including MuSK-MG), completed in 2019. Preliminary results, yet unpublished, showed no safety concerns but did not achieve a significant improvement in MG scores. Further research through large-scale and long-term clinical trials is crucial to understand the effectiveness of iscalimab fully.

Indirect Targeting

Cytokines such as B lymphocyte stimulating factor (BAFF, also known as BLyS and TNFSF13b), proliferation-inducing ligand (APRIL, TNFSF13), and their receptors play a crucial role in the growth, development, maturation, and homeostasis maintenance of B cells. Indirectly targeted therapies reduce the counts of, or eliminate, B cells and alleviate clinical symptoms in patients by blocking the functions of cytokines, such as BAFF and APRIL, or targeting plasma cell proteasome inhibitors (Figure 3).

B Cell Activating Factor BAFF (Belimumab)

Belimumab is a recombinant human IgG1λ mAb that neutralizes the soluble form of BAFF, a key B cell activating factor. It includes membrane-bound and secreted BAFF variants produced by non-B cells, such as monocytes, dendritic cells, and macrophages.[64] BAFF binds to three different receptors: (1) BAFF receptor (BAFFR, also known as BR3 and TNFRSF13C) is mainly expressed on mature B cells; (2) B cell maturation antigen (BCMA, TNFRSF17) is only on plasma cells; and (3) transmembrane activator, calcium regulator, and cyclophilin ligand interactor (TACI, TNFRSF13B) are present on activated B cells, marginal zone B cells, switched memory B cells, and plasma cells.[65–69] The dysregulated expression of BAFF affects the activation, proliferation, survival, and immunoglobulin secretion of B cells, thereby affecting the development of autoimmune diseases.[70] BAFFR mediates BAFF survival signals. When BAFF binds to BAFFR, it activates the NF-κB pathway, leading to the transcription of the anti-apoptotic factor Bcl-2, whose expression is essential for the survival of B cells as they transition from immature to mature stages.[71,72] Belimumab is the sole biological drug approved by the FDA to treat systemic lupus erythematosus (SLE) by targeting B cells. It blocks BAFF-BAFFR signaling by binding to soluble BAFF and promotes apoptosis of B cells.[73] In a multicenter phase 3 trial, Belimumab demonstrated modest efficacy in patients with SLE.[74,75] Whereas, in a phase 2 placebo-controlled,

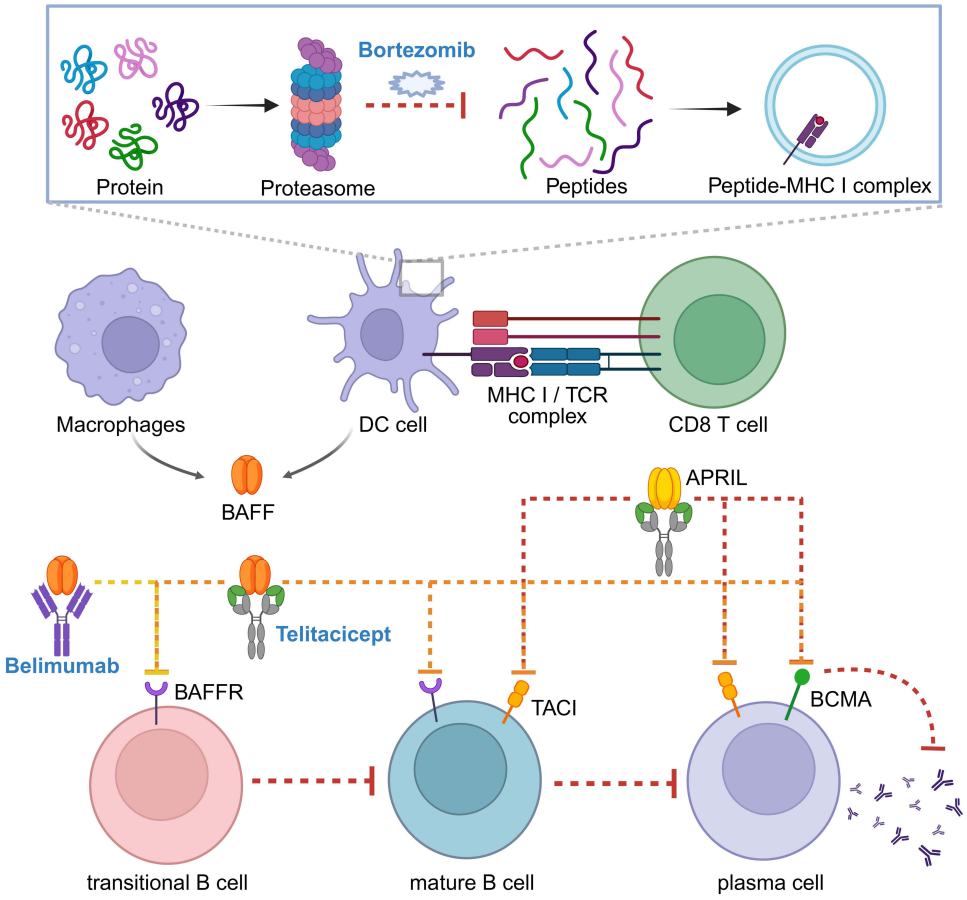

Figure 3 Mechanism of action of indirect B cell-targeting drugs. Belimumab affects B cell survival by blocking B lymphocyte stimulating factor (BAFF)-BAFF receptor (BAFFR) signaling by binding to soluble BAFF. Telitacipep can simultaneously target BAFF and April, multi-stage inhibiting the maturation and differentiation of B cells. Bortezomib binds to 26S proteasome to inhibit its enzymatic activity and leads to reducing the degradation of intracellular proteins, affecting the activation of T-cells, and promoting plasma cell apoptosis. (Image created with BioRender.com).

multicenter, double-masked study (NCT01480596), the patients with generalized MG who were receiving standard treatment did not reach the primary outcome, with no significant differences in Activities of Daily Living and Quantitative Myasthenia Gravis scores at week 24 compared with the placebo group. This effect was not observed significantly in patients with MuSK-MG.[76]

Inhibition of B Cell Proliferation, Differentiation, and Activation (Telitacicept)

Telitacicept is a TACI-Fc fusion protein, composed of the extracellular specific soluble part of TACI and the Fc part of human IgG1. It can simultaneously target BAFF and APRIL to inhibit the maturation and differentiation of B cells at multiple stages.[77,78] BAFF and APRIL are two trimeric members of the tumor necrosis factor (TNF) family that are expressed in varieties of cell types.[65] They are the key to stable B cells and the humoral immune proteins B cells. They combine with different receptors on B cells and plasma cells, and BAFF and APRIL both combine with TACI and BCMA. The difference is that BAFF also combines with BAFFR, but APRIL does not.[65,66] BAFF is essential for the survival, differentiation, and maturation of B cells, while APRIL has a greater impact on regulating the function and survival of long-lived plasma cells, thereby affecting the production of antibodies.[77] Telitacicept can recognize and bind to BAFF and APRIL, blocking their interactions with TACI, BCMA, and BAFFR, thereby inhibiting B cell proliferation and T cell maturation.[77] In 2024, data from a multicenter, randomized, open-label phase 2 clinical study by Professor Fang Jianmin et al[77] and Professor Li Zhijun et al[79] showed that telitacicept, as a dual inhibitor of BAFF and APRIL, not only showed significant efficacy and was able to improve patients' clinical symptoms, but also showed good tolerability and safety. Most adverse events were classified as mild or moderate, with no serious adverse reactions. The results also

suggest that telitacicept may have long-term efficacy and maintain therapeutic effects even after treatment.[77,79] A multicenter, randomized, double-masked, placebo-controlled phase 3 study of telitacicept (NCT05737160) is underway and is expected to be completed in 2027.

Proteasome Inhibitors (Bortezomib)

Bortezomib is a novel proteasome inhibitor that exerts its immune effects by affecting the survival of plasma cells. Its primary mechanism of action is to inhibit the normal function of proteasome responsible for protein degradation in the nucleus, thereby causing protein accumulation in the cell, leading to cell cycle arrest and apoptosis.[80,81] The inhibition of proteasome function by bortezomib is particularly detrimental to the normal survival of cells with high protein turnover. Plasma cells have a high protein turnover due to the continuous release of antibodies, and they are highly sensitive to proteasome inhibitors, which can lead to the accumulation of immunoglobulin chains, which then leads to plasma cell apoptosis.[82] Bortezomib is approved for the treatment of multiple myeloma and is a potential treatment option for autoimmune diseases that are resistant to various standard treatments, including generalized MG.[82] A patient with MuSK-MG who had a poor response to conventional immunotherapy and RTX experienced rapid and sustained improvement after treatment with bortezomib.[83] In 2014, a nonrandomized clinical trial (NCT02102594) evaluating bortezomib for antibody-mediated autoimmune diseases, including MuSK-MG, was discontinued due to recruitment difficulties; therefore, the efficacy of bortezomib in MG needs further study.[84] The drug is associated with neurotoxicity and subsequent disabling peripheral neuropathy.[85–87] This neurotoxicity is dose-dependent, but the risk of neuropathy can be reduced by adjusting the dose and the mode of administration.[88]

CAR-T Cell Therapy

Chimeric antigen receptors (chimeric antigen receptor, CAR) are synthetic proteins designed to reprogram T cells, The CAR structure consists of an extracellular antigen-recognition component (single-chain variable fragment), a transmembrane region, an intracellular costimulatory domain (typically 4–1BB or CD28), and a CD3 intracellular signaling domain (Figure 4a).[89,90] CAR-T therapy modifies T cells to specifically recognize and eliminate cells expressing specific antigens (Figure 4a). In recent years, CAR-T therapy has made significant progress in the field of hematological malignancies, and has been gradually applied to the treatment of autoimmune diseases.[91] An earlier phase

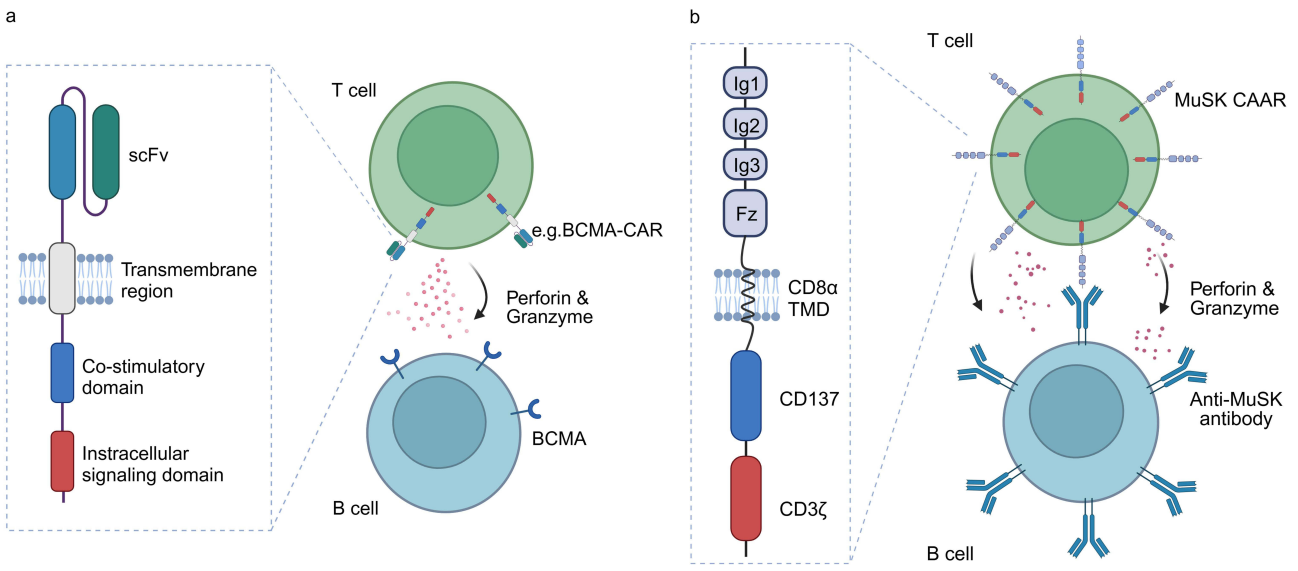

Figure 4 The structure and mechanism of CAR-T and MuSK-CAAR-T. (**a**) The CAR is composed of an extracellular antigen-recognition component (scFv), a transmembrane region, an intracellular costimulatory domain, and an intracellular signaling domain. CAR-T cells can specifically recognize and produce cytotoxic perforin/granzyme to eliminate B cells expressing specific antigens. (**b**) MuSK-CAAR is composed of the extracellular domain of the MuSK protein, the CD8 transmembrane domain, and the CD137-CD3ζ intracellular stimulating and signal transduction domain structure. T cells expressing MuSK-CAAR specifically recognize B cells expressing MuSK-specific antibodies or BCR and elicit cytotoxic effects against them. (Image created with BioRender.com).

1 study (NCT04561557) showed that two patients (one AChR-MG and one MuSk-MG) with highly relapsed and refractory MG showed favorable safety and sustained clinical improvement over 18 months after treatment with BCMA-targeting CAR-T cells.[92]

CAT-T therapy has great potential in autoimmune diseases, but the associated toxicity and the need for lymphocyte depletion limit its use in patients with autoimmune diseases. To improve the safety of CAR-T therapy, Granit et al[93] used an RNA (rCAR-T) rather than a DNA approach to engineer T cells to target BCMA on the plasma cell surface and attempted to use rCAR-T to treat patients with MG. Unlike conventional DNA-engineered CAR T cells, their RNA-engineered counterparts do not persist for long and do not require demanding lymphocyte depletion protocols. In a prospective, multicenter, open-label, nonrandomized phase 1b/2a study of rCAR-T in MG (NCT04146051), Descartes-08 was reported to be safe and well tolerated, with clinically meaningful improvements observed at up to 9 months of follow-up. There were no adverse events (eg, cytokine release syndrome) that were similar to those seen with DNA CAR T cells.[93]

CAAR-T Cell Therapy

Patients with acquired autoimmune diseases harbor antigen-specific autoreactive B cells in their bodies. These B cells express BCRs on their surfaces that are capable of binding specifically to their target antigens, a feature absent in normal B cells. Studies have shown that B cells can rapidly internalize their cognate antigens upon contact. This specificity of BCR antigens forms the basis of reverse BCR-targeted therapy, known as BAR (BCR antigen for reverse targeting). This approach enables targeted recognition and elimination of B cells expressing specific BCRs. Recently, BAR has been successfully applied to the precise elimination of antigen-specific B lymphocytes associated with several autoimmune diseases.

CAAR-T cell therapy is a further refinement of CAR-T therapy, which is specifically designed to target B cells that produce pathogenic antibodies. The recombinant autoantibody receptor of CAAR-T cells replaces the single-chain variable fragment (scFv) antigen recognition domain of CAR-T cells. This modification allows CAAR-T cells to precisely target the specific BCR on the surface of B cells, thereby selectively eliminating antigen-specific B cells without affecting normal B cells (Figure 4b).[94,95] In model animals, reinfusion of CAAR-T cells can significantly reduce the titer of autoantibodies without affecting other B cells. This approach aims to avoid the chronic immunosuppression associated with current treatments and potentially offer therapeutic efficacy comparable to or superior to CAR-T therapy. In 2023, Sangwook Oh et al designed MuSK chimeric autoantibody receptor (MuSK-CAAR)-T cells incorporating a CD137-CD3ζ signaling domain to precisely target B cells that express anti-MuSK autoantibodies (Figure 4b). Their results showed that MuSK-CAAR-T cell treatment in the mouse model of MuSK-MG reduced the anti-MuSK antibody levels but did not affect the overall B cell counts or IgG levels, reflecting the depletion of MuSK-specific B cells.[95] Furthermore, recruitment is currently underway for a phase 1, open-label study (NCT05451212) initiated by Cabaletta Bio in November 2022 to evaluate the safety of various dosing regimens for the treatment of MuSK-MG. This study is expected to be completed by 2028.

Outlook: Advantages, Limitations, and Challenges Associated with B Cell-Targeted Therapy for MuSK-MG

MuSK-MG is a serious and intractable NMJ disease. Establishing strategies for the precise and effective treatment of MuSK-MG, especially for patients with refractory MG is urgently needed. Compared with traditional immunotherapy methods, B cell-targeted therapy is expected to improve patients' clinical symptoms while minimizing side effects and enhancing patient compliance more precisely and rapidly.

Direct B cell-targeted therapy offers several advantages. For example, monoclonal antibodies exhibit high specificity and provide lasting and potent therapeutic effects by directly eliminating B cells without affecting other immune cells. In addition, they are associated with fewer off-target effects. However, one of the limitations associated with their use is their inability to distinguish between normal and autoreactive B cells, which potentially compromises normal humoral immunity. Furthermore, their effectiveness may vary as they cannot comprehensively eliminate autoreactive B cells

across different developmental stages. Indirect B cell-targeted therapy functions mainly through immune regulation, lacking direct B cell elimination capabilities. In a phase 2 clinical study, telitacicept has shown significant efficacy and good safety by inhibiting B cell maturation and differentiation at multiple stages. However, it does not completely eliminate autoreactive B and plasma cells.

CAR-T therapy has shown the light of cure in the treatment of MG. However, the neurotoxicity, cytokine release syndrome (CRS), hypogammaglobulinemia and other related toxicities of DNA CAR-T therapy, and the need for lymphocyte depletion have limited its application in autoimmune diseases. To improve the safety of CAR-T therapy, Granit et al[93] designed rCAR-T, which is the expression of CAR through RNA engineering. Because the CAR-encoding mRNA does not replicate with activated and proliferating rCAR-T cells, amplification of the CAR signal is avoided, and the CAR+ load is dose-dependent and decreases over time, enabling more precise pharmacokinetic control and reducing the potential hematologic toxicity and tumor risk of genomic integration. In addition, since this method uses ex vivo T cell proliferation, there is also no need for depletion of lymphocytes to induce a specific cytokine milieu prior to administration. At present, CAR-T cell therapy provides a potential revolutionary treatment for immune-mediated nervous system diseases, bringing new hope for patients who fail to respond to traditional treatment. Although more clinical trials are needed to verify its safety and efficacy, and further research is needed to optimize the treatment regimen and reduce the cost of treatment. However, the long-term remission potential of CAR-T cell therapy and the advantages of individualized treatment indicate that it may become a powerful tool for the treatment of such diseases.

CAAR-T therapy represents a cutting-edge precision medicine approach. It selectively targets immune cells expressing specific autoantibodies, such as those seen in MuSK-MG, without inducing broad immunosuppression. Preclinical studies in mouse models have shown that CAAR-T cells selectively eliminate MuSK-specific B cells, demonstrating potential for use as targeted therapies for treating MuSK-MG. While both MUSK-CAART and CAR-T target the BCR complex on plasma cells and kill plasma cells, MUSK-CAART chimeric autoantigen MuSK receptors that bind specifically to the variable region of the BCR and kill only plasma cells that produce antibodies against MuSK. In contrast to CAR-T (which kills all plasma cells), MUSK-CAART chimeric autoantigen MuSK receptors bind specifically to the variable region of the BCR and kill only plasma cells that produce antibodies against MuSK. It has obvious advantages. However, the circulating autoantibodies could significantly affect the treatment of CAAR-T, and further studies are still needed to optimize the treatment plan. Although their use comes with a few challenges, including the requirement for demanding and expensive procedures for the in vitro engineering and expansion of patient-specific autologous T cells; this limits the widespread clinical application of CAAR-T cells. However, it has great potential research value in the treatment of autoimmune diseases.

In summary, many promising B cell-targeted therapies for MuSK-MG have encountered setbacks during preclinical and clinical development stages. These failures are primarily due to weak immunosuppressive reactions, nonspecific immunogenicity, or security issues. Although currently used targeted therapies in clinical settings are effective, they are also associated with limitations. Thus, exploring and identifying more precise approaches to improve the efficacy and safety of these critical therapies is needed. Strategies such as targeting only antigen-specific B cells, combination therapies addressing multiple targets, antibody-drug conjugates, and dual-targeted drugs that circumvent the need for autologous T cell modification hold promise for developing disease-specific targeted therapies.

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