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Advances and challenges in the treatment of myasthenia gravis

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***Abstract*:** Myasthenia gravis (MG) is a chronic autoimmune disease with fluctuating muscle weakness and fatigability. Standard immunomodulatory treatment may fail to achieve sufficient improvement with minimal symptom expression or remission of myasthenic symptoms, despite adequate dosing and duration of treatment. Treatment-resistant MG poses a challenge for both patients and treating neurologists and requires new therapeutic approaches. The spectrum of upcoming immunotherapies that more specifically address distinct targets of the main immunological players in MG pathogenesis includes T-cell directed monoclonal antibodies that block the intracellular cascade associated with T-cell activation, monoclonal antibodies directed against key B-cell molecules, as well as monoclonal antibodies against the fragment crystallizable neonatal receptor (FcRn), cytokines and transmigration molecules, and also drugs that inhibit distinct elements of the complement system activated by the pathogenic MG antibodies. The review gives an overview on new drugs being evaluated in still ongoing or recently finished controlled clinical trials and drugs of potential benefit in MG due to their mechanisms of action and positive effects in other autoimmune disorders. Also, the challenges associated with the new therapeutic options are discussed briefly.

Keywords: B-cell directed therapies, CAR-T-cell therapy, complement-inhibitors, FcRn-inhibitors, immunotherapy, interleukin-inhibitors, MG, myasthenia gravis, refractory myasthenia gravis

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Introduction

The main reason for the development of new therapeutic strategies in MG is the need for more specific and more effective drugs in particular in so-called refractory or difficult-to-treat/treatment resistant autoimmune myasthenia gravis.[1,2] The inability to achieve sufficient clinical improvement with minimal symptom expression or remission of myasthenic symptoms despite adequate dosing and sufficient treatment duration of standard immunomodulatory treatment in all MG patients poses a challenge for both patients and treating neurologists, and illustrates the need for new therapeutic strategies. The recent awareness of the unmet needs in MG has in part been driven by studies of new pharmacotherapies in which patients with MG not fully responding to standard immunosuppressive treatment were recruited.[3,4] Standard previous treatment included corticosteroids in combination with azathioprine or other immunosuppressants such as cyclosporine A, mycophenolate mofetil, tacrolimus or methotrexate, given in an adequate dose and over a sufficiently long time period.[5] The aim of this review is to present the spectrum of emerging new immunotherapies in MG.

The spectrum of upcoming immunotherapies with a more specific action on the immune system includes T-cell directed monoclonal antibodies that block the subsequent intracellular cascade associated with T-cell activation, monoclonal antibodies directed against key B-cell molecules, and monoclonal antibodies directed at the fragment crystallizable neonatal receptor (FcRn), as well as inhibition of distinct elements of the complement

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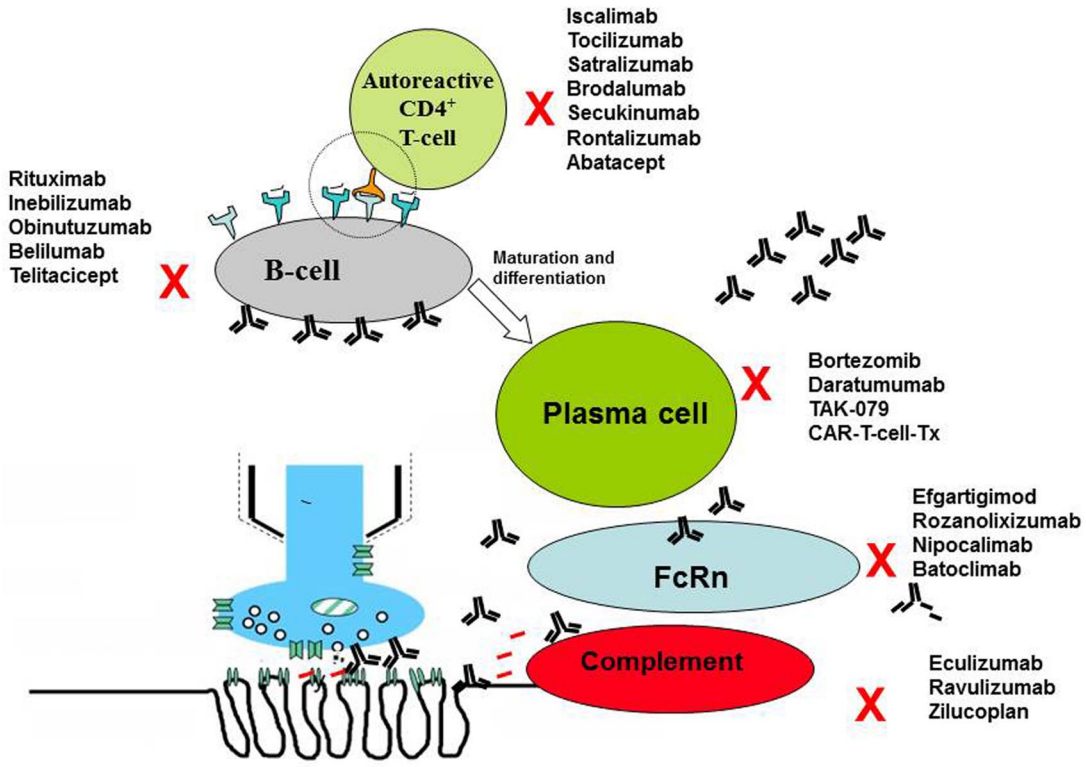

Figure 1. New immunotherapies in myasthenia gravis.

system (shown in the Figure 1 and in the Table 1). Some of these drugs have been recruited from the therapeutic arsenal recently developed for treatment of other autoimmune or neoplastic diseases.[6] In the last few years, several clinical studies have been conducted to study safety, tolerability and efficacy of the new substances in MG, some trials are still ongoing or planned (see Table 1). In order to understand which new therapeutic agents should be considered as most promising in future MG therapy, it seems appropriate to briefly describe key aspects of the MG pathophysiology. The review aims at giving an overview on recent developments in the field of new therapeutic substances in MG to elucidate their mechanisms of action, describe ongoing studies and briefly list some of the challenges.

Pathophysiology of myasthenia gravis

MG is a prototypic autoimmune disease in which several types of autoantibodies (abs) directed against distinct proteins of the neuromuscular endplate have been identified. MG can be divided into seropositive MG with abs directed either against the nicotinergic acetylcholine receptor (AChR), muscle tyrosine kinase (MuSK) or low density lipoprotein receptor type 4 (LRP4), and seronegative MG where no such antibodies are detected by available methods. The pathophysiological relevance of several other muscle antibodies that may be detected in some MG patients, including abs against agrin, cortactin, collQ, acetylcholinesterase (AChE), Kv1.4, titin and ryanodine receptor has not been delineated so far.[7–9] In up to 80% of patients with generalized MG, abs against the nicotinergic type of AChR are present, whereas abs directed against MuSK or LRP4 are detectable in about 6% and 2% of the generalized MG-patients only, with population variation.[10]

Role and function of specific antibodies

The different types of ab act differently at the neuromuscular endplate, determining different types of immunopathology, and in turn also the response to treatment. This is in particular true for AChR-ab and MuSK-ab positive MG. The determination of IgG subclass type for the pathogenic abs may have implications for treatment strategies. AChR-abs which belong to subclass IgG1, IgG2, or IgG3 induce internalization and

Table 1. Some drugs addressing cellular and molecular targets that may be relevant as therapy for generalized myasthenia gravis.

Group of therapeutic agents **B-cell- and plasma cell-directed therapies**	Target	Type of drug	Effect/mechanism	Study in MG/ MG-Type
Rituximab	CD 20	Chimeric IgG monoclonal ab	Depletion of CD 20 cells	Phase II study (Beat MG) AChR and MuSK
Inebilizumab	CD 19	Humanized IgGκ monoclonal ab	Depletion of CD 19 cells	Phase III study AChR and MuSK (NCT04524273) ongoing
Obinutuzumab	CD 20	Humanized monoclonal ab	Cell death of CD 20 cells	No study
Belilumab	B-lymphocyte stimulator (called BLyS, BAFF or TNFSF13B)	Human monoclonal IgG1λ ab	Reduction in B cell differentiation, reduction of circulating CD 19 cells	Phase II study AChR and MuSK Published
Iscalimab	CD 40 expressed on B-cells, T-cells and APC (ligand CD 154 on activated T cells)	Human Fc silenced IgG1 monoclonal ab	Blocking of T-cell dependent antibody responses and germinal cell formation	Phase II study (add on therapy) AChR and MuSK (NCT02565576)
Telitacicept	BLys and APRIL	TACI-Ig fusion protein	Reduction of mature B-cells	Phase II study AChR and MuSK (NCT04302103) Ongoing
Bortezomib	Proteasome (Plasma cells)	Proteasome inhibitor	Inhibition of plasma cell/long lived B cell proliferation, reduced T-cell activation and proliferation reduced TNF-α, IL-1β, IL-6, NFkB production reduced CD 20-degradation	Open clinical study unpublished
Tak-079/Mezagitamab	CD 38 expressed on plasma cells, T- and NK-cells	Human monoclonal IgG1 ab	Reduction of plasma cells, T- and NK- cells	Phase II study AChR and MuSK, (NCT04159805) ongoing
Daratumumab	CD 38	Human monoclonal IgG1κ ab	Reduction of plasma cells, T- and NK- cells	No study
Complement inhibitors				
Eculizumab	C5	Humanized monoclonal ab	Inhibition of terminal complement/MAC activation	Phase III study AChR published
Zilucoplan	C5/C5b	Short 35 kDa macrocyclic peptide	Inhibition of terminal complement/MAC activation	Phase II study AChR published
Ravulizumab	C5	Humanized IgG2/4 monoclonal ab	Inhibition of terminal complement/MAC activation	Phase III study (NCT03920293) AChR ongoing

(Continued)

Table 1. (Continued)

Group of therapeutic agents B-cell- and plasma cell-directed therapies	Target	Type of drug	Effect/mechanism	Study in MG/ MG-Type
FcRn-antagonists				
Efgartigimod	FcRn	Anti-FcRn-IgG1 Fc fragment	Inhibition of IgG3 > IgG4 autoantibody recycling, reduction of auto ab levels	Phase III study (i.v.) AChR and seroneg. published Phase II study s.c. vs. i.v. ongoing NCT04735432
Rozanolixizumab	FcRn	Human anti FcRn IgG4 ab	Reduction of auto ab levels	Phase II study AChR and MuSK published
Batoclimab	FcRn	Human monoclonal ab	Reduction of auto ab levels	Phase II study AChR (NCT03863080) unpublished
Nipocalimab	FcRn	Human deglycosylated IgG1 anti-FcRn monoclonal ab	Reduction of auto ab levels	Phase II study AChR and MuSK (NCT03772587) Ongoing
T cell directed therapies				
Tocilizumab	Il-6R	Humanized IgG1 monoclonal ab	IL-6R signaling blockade, inhibition of T-cell activation	No study
Satralizumab	IL 6R (soluble and membrane bound)	Humanized IgG2 monoclonal ab	IL-6R signaling blockade, inhibition of T-cell activation	Phase III study AChR (NCT04963270) ongoing
Brodalumab	IL-17RA	Monoclonal IgG2κ ab	Inhibition of interaction of IL17RA with IL-17A, IL-17 F, IL-17 C, IL-17A/F and IL-25	No study
Secukinumab	IL-17	Monoclonal IgG1 ab	Binding to IL-17A and inhibition of interaction of IL-17A and IL-17R	No study
Rontalizumab	INF alpha	Humanized monoclonal ab		No study
Abatacept	CD 80/CD 86	Fusion protein Fc part of IgG1 + extracellular domain of (CTLA4)	Inhibition of co-stimulation of T-cells by antigen-presenting cells	No study
Chimeric antigen receptor (CAR)-T-cell therapy	plasma cells expressing BCMA	Autologous T-cells directed against BCMA	Elimination of plasma cells expressing BCMA	Phase Ib/IIa study ongoing Descartes-08(NCT04146051) AChR and MuSK

AChR, acetylcholine receptor; APC, antigen presenting cell, APRIL, a proliferation-inducing ligand; BAFF, B-cell activating factor; BCMA, B-cell maturation antigen; BLyS, B-lymphocyte stimulator; CAR, chimeric antigen receptor; CD, cluster of differentiation; IgG, immunoglobulin G; IL-1β, interleukin 1 beta; IL-6, interleukin 6, MAC, membrane attack complex; MG, Myasthenia gravis; MuSK, muscle tyrosine kinase; NK, natural killer; TACI, transmembrane activation and calcium modulator and cyclophilin ligand interactor; TNF-α, tumour necrosis factor alpha.

degradation of AChR by crosslinking the receptors in the postsynaptic region. An important effector mechanism, in particular of IgG1 and IgG3 AChR-abs, is complement activation leading to destruction of neuromuscular endplate structures by the membrane attack complex (MAC), and including loss of postsynaptic folding, reduction of AChRs in the membrane and an increase of the intersynaptic distance, altogether impairing neuromuscular transmission.[7–9,11] A third, but less important mechanism is direct ab-blockade of the AChR. AChR-abs are mainly generated by long-lived plasma cells.[7–9] Clinically, AChR-ab positive MG is subtyped as pure ocular versus generalized MG with or without bulbar involvement and with early onset or late onset (before or after age 50 years), and with or without thymoma.[5]

MuSK is a key molecule with regard to AChR clustering.[7–9] MuSK abs disrupt the interaction of LRP4 with MuSK, required for clustering of the AChR. These abs can induce the dispersion of preformed agrin-independent AChR clusters.[11] Thus, the molecular structure underlying the endplate region becomes severely disturbed. MuSK abs are of subclass IgG4, and unable to activate complement. They are thought to be produced by short-lived plasma blasts which is in accord with the better response to rituximab in MuSK-ab positive than in AChR-ab positive MG.[6,12] LRP4 abs belong to the complement activating IgG1 and IgG3 subclass, and can disrupt agrin-LRP4 signaling in the postsynaptic membrane.[7,9,11,13]

In seronegative MG there is in some patients evidence for IgG1 antibodies directed against clustered AChR capable to activate complement and correlating with complement deposits in patients' thymus tissue and with typical electrophysiological MG features.[14,15] Intercostal muscle biopsies in seronegative MG revealed complement deposits activated by IgG1.[16]

Mechanisms of action of therapeutic agents in MG

MG treatments act at various steps of the immune cascade. Main mechanisms of action include reduction of T- and B-cell proliferation (steroids, azathioprine, mycophenolate mofetil), reduction of T-cell proliferation (cyclosporine A, tacrolimus, methotrexate), depletion of short-living B-cells (rituximab), depletion of long-living B-cells (bortezomib), complement-inhibition (eculizumab, ravulizumab, zilucoplan).[6] Plasma exchange and immunoadsorption aim at rapid elimination of pathogenic abs and complement, and IvIG inhibit complement activation and pathogenic abs.[5,17] Thymectomy is a standard procedure in early onset AChR-ab positive MG under age of 50. Its efficacy regarding long-term improvement has been demonstrated by a randomized study in which 126 patients, 66 treated by thymectomy and steroids and 60 treated by steroids only were included, and also in several real-life, uncontrolled studies.[5,10,18] It is of crucial importance to remove surgically all thymic tissue. Thymectomy is now often performed by an endoscopic procedure.[5] In MuSK-antibody positive myasthenia gravis thymectomy apparently does not seem to lead to clinical improvement.[19]

Difficult to treat or refractory MG

The definition of difficult to treat or refractory MG is still under debate, but there is some consensus that main characteristics are persistent impairment in activities of daily living; at least one imminent or apparent myasthenic crisis per year (not related to lack of compliance, infection, or use of drugs that induce MG deterioration), a regular need for plasma exchange or IVIg; or persistent major side effects of MG treatment. This should occur despite adequate standard treatment including thymectomy if indicated, acetylcholine esterase (AChE) inhibitors at maximum tolerable doses, corticosteroids in an acceptable dose; and use of at least two standard immunosuppressants in a sufficient dose for $\geqslant 1$ year.[1,2]

B-cell directed therapies

B-cells play a decisive role in the pathogenesis of MG. Therefore, therapeutic approaches targeting key molecules of B-cells, mainly CD 19 and CD 20, are expected to be effective in MG. Rituximab is a chimeric monoclonal antibody against the B cell surface antigen CD20. This drug depletes CD20 positive B- cells for 6–12 months, mainly due to apoptosis and receptor down-regulation. Immune effects include reduction of antigen presentation, reduced cytokine production, T-cell and macrophage activation, as well as upregulation of Treg cells.[6,12] Rituximab for MG is not regarded as off-label in many countries and has been administered to patients with AChR-ab and MuSK-ab positive MG in the last 15 years.[4–6]

Several observational studies indicate that both MuSK-ab positive and AChR-ab positive patients profit from regular administration of rituximab.[20–26] The drug seems in some patients to be effective even at low doses of 250 to 500 mg given every 6–9 months.[4,27,28] Evidence from prospective and controlled studies for a positive effect of rituximab in MG is still lacking. The phase II Beat-MG trial failed to prove efficacy, in particular a steroid sparing effect, of rituximab in a larger cohort of MG patients, probable related to the baseline criteria of patients included into the study, to the study design, and drug-related mechanisms.[7,29] Nevertheless patients with MuSK-ab positive MG appear to have better outcomes with rituximab than their counterparts with AChR-ab positive MG.[22,30,31]

Inebilizumab is an i.v. administered humanized IgG kappa monoclonal ab targeting the CD19 surface antigen on B-cells. In contrast to rituximab, inebilizumab depletes a broad spectrum of B cells including plasmablasts and some plasma cells. A placebo-controlled trial in NMO spectrum disease showed positive effects with less relapses in the treatment group suggesting that inebilizumab might become a B-cell directed treatment option also in MG.[31,32] A multicenter study evaluating inebilizumab in AchR-ab and MuSK-ab positive myasthenia gravis is ongoing.[33]

Obinutuzumab, an anti-CD 20 monoclonal ab leading mainly to direct cell death of B-cells, was administered to a single patient with chronic lymphatic leukemia and treatment resistant MG, leading to substantial improvement of myasthenic symptoms.[34]

B-cell proliferation and survival are regulated by B-cell activating factor/a proliferation-inducing ligand (BAFF/APRIL), B-cell activating factor receptor (BAFF-R), B-cell maturation antigen (BCMA), and transmembrane activation and calcium modulator and cyclophilin ligand (CAML) interactor (TACI).[35] A phase II study on telitacicept (TACI-Ig fusion protein) in MG is ongoing (NCT04302103).[36] Telitacicept (RC18) acts by binding to two cell-signaling molecules, B-lymphocyte stimulator (BLyS) and a proliferating-inducing ligand (APRIL). By only affecting mature B cells, telitacicept has minimal impact on early and memory B cells, which are important for an adequate body immune function.[35] Belimumab, a human monoclonal IgG1λ ab directed against B-lymphocyte stimulator (called BLyS, BAFF or TNFSF13B), induces a reduction in B-cell differentiation and thereby leads to a reduced number of circulating CD 19 cells.[37] However, this drug did not show a significant positive effect as adjunctive treatment in a randomized and placebo-controlled study of generalized MG.[38] Further B-cell directed therapies are under development or have already been approved for other B-cell mediated autoimmune diseases.[35,37]

Plasma cell directed therapies

Based on experimental studies, the proteasome inhibitor bortezomib should be promising as a new therapeutic agent in MG as this drug induces cell death and reduction of plasma cells, T-cell activation and proliferation, and secretion of TNF-α, IL-1β, and IL-6.[39] Bortezomib is a selective reversible inhibitor of the 26 s proteasome, effective in the elimination of malignant plasma cells in multiple myeloma, and in particular in the depletion of short-lived and long-lived B-cells and plasma cells.[40] Plasma cells produce the pathogenic antibodies in MG. In a few cases, bortezomib 1.3 mg/m^2 body surface s.c. four times within 2 weeks led to improvement of severe, refractory MG.[41] An open trial of bortezomib in autoimmune disease including MG was stopped due to recruitment problems.[42]

TAK-079 is a monoclonal ab against CD38 expressed on plasma cells, T and NK-cells and represents a potential drug in MG therapy. A phase II study in AChR- and MuSK-ab positive MG patients has started in 2020 (NCT04159805).[37,43] Daratumumab, another CD 38 ab, is approved for multiple myeloma and may represent an alternative drug to reduce plasma cell activity in MG.[6]

Complement inhibitors

The complement system represents an important part of the innate immune system. In autoimmune complement-mediated diseases, specific autoantibodies activate complement which leads to damage of distinct tissue-specific structures, for example, the neuromuscular endplate in AChR-antibody positive MG. Complement inhibitors like eculizimab, ravulizumab and zilucoplan may reduce terminal complement/MAC activation in MG by blocking C5 and in case of zilucoplan also C6.[44]

Eculizumab is a monoclonal antibody directed against C5, and previously established as therapy of complement-mediated disorders like hemolytic uremic syndrome and paroxysmal nocturnal hemoglobinuria. After the REGAIN study had shown rapid and functionally important improvement in refractory AChR-ab positive MG, also other complement inhibitors have been considered as a therapeutic option in MG.[3] REGAIN showed efficacy of eculizumab ($n = 62$) vs placebo for secondary endpoints including the Quantitative Myasthenia gravis Score (QMG)), MG-Quol 15, proportion of patients with at least a 3-point reduction in the MG-ADL score, but not for the primary MG-ADL endpoint ($p = 0.069$). Most patients improved during the first 12 weeks and remained stable during treatment with 1200 mg eculizumab every 2 weeks till week 130 in the open label extension study.[3,45] Rates of exacerbations, rescue therapies and hospitalization were significantly lower in the eculizumab group compared to the placebo group.[3,45]

Ravulizumab is a humanized monoclonal ab functionally similar to eculizumab. Ravulizumab has a prolonged half-life due to enhanced FcRn binding and is administered iv every 8 weeks. Currently, a phase 3 study on ravulizumab in MG is ongoing.[46]

Zilucoplan is a short 35 kDa macrocyclic peptide which binds to C5, blocks C5 cleavage into C5a and C5b, and prevents therefore binding of C5b to C6 thereby inhibiting the activation of MAC. In a randomized, double-blind, placebo-controlled phase 2 clinical trial, 44 AChR-ab–positive patients with generalized MG and mean baseline Quantitative Myasthenia Gravis (QMG) score of 18.8 were randomized to a daily s.c. self-injection of placebo ($n = 15$), 0.1 mg/kg zilucoplan ($n = 15$), or 0.3 mg/kg zilucoplan ($n = 14$) for 12 weeks.[46] Zilucoplan 0.3 mg/kg resulted in a mean reduction from baseline of 6.0 points in the QMG score and 3.4 points in the MG ADL score. Near-complete complement inhibition appeared superior to submaximal inhibition.[47]

Further complement inhibiting substances may be transferred from other indications to the MG field in the future.

FcRn antagonists

Fragment crystallizable neonatal receptor (FcRn) is a MHC-like receptor that binds albumin and IgG and protects IgG from its lysosomal degradation by transporting it back to the cell surface to reenter the circulation (IgG recycling). This mechanism extends IgG life span, in particular that of IgG3, and is more effective in increasing the IgG serum concentration than IgG production. In ab-mediated diseases, this physiologic mechanism maintains disease activity by preserving autoantibodies. IgG recycling contributes to a delay or lack of therapeutic efficacy of immunomodulators acting at upstream levels of the immune cascade. In turn, inhibition of FcRn appears to be a promising mechanism to prevent antibody-mediated effects in autoimmune disease. The extent of IgG recycling is related to the functional status of FcRn.[48,49]

Drugs targeting FcRn lead to reduction of FcRn expression and availability with inhibition of FcRn function. This leads to increased degradation of endogenous IgG including pathogenic autoantibodies. FcRn inhibitors bind to FcRn with high affinity and lead to selective reduction of serum IgG, preferentially of IgG 3 and to a lesser extent of IgG4, but also to some albumin reduction. The effects of FcRn inhibition are reversible and related to dose. The IgG reduction is typically up to 70%–90% of what is obtained by plasma exchange. FcRn inhibition has no effects on other components of the immune system, in particular no influence on B-cells and plasma cells.[4] A few FcRn inhibitors have already been evaluated in clinical trials in MG:

Efgartigimod is a humanized anti-FcRn-IgG1 Fc fragment. In the phase III ADAPT study, a single dose of efgartigimod 10 mg/kg body weight i.v. reduced serum IgG and AChR abs by up to 50% within the first 2 weeks, correlating with significant clinical improvement.[50] Continuous treatment reduced serum IgG and AChR abs by a maximum of 75%. The AChR-ab and IgG reduction correlated with the extent and duration of clinical improvement. Two-thirds of the patients showed significant improvement of MG-ADL as compared to placebo. In the MG group without detectable antibodies, 9/19 patients showed ADL and QMG response compared to only 4 patients in the placebo group. An ongoing study examines whether efgartigimod given subcutaneously has the same beneficial effect.[51]

Rozanolixizumab, a human anti FcRn IgG4 ab, was shown to reduce plasma IgG by 75%–90%

when 50 mg or 150 mg/kg doses were administered in a phase 2 trial in MG, but the drug did not induce clinically significant improvement of the QMG) as primary endpoint but of secondary endpoints (MG ADL, MGC-Score).[52] This might be attributed to the design of the trial. Nipocalimab is a human deglycosylated IgG1 anti-FcRn monoclonal ab that binds with picomolar affinity to FcRn at both endosomal pH 6.0 and extracellular pH 7.6.[6,49] It seems to be safe in pregnant women. A phase II trial in AChR- and MuSK ab positive MG is ongoing (NCT03772587).[53] The results of another FcRn-inhibitor phase II study, in which batoclimab (RVT-1401) was evaluated in MG, have not been published so far.[54]

T-cell directed treatments

Iscalimab, an anti-CD40 monoclonal ab, expressed on B-cells, T-cells, and antigen-presenting cells leads to blockade of T cell dependent ab responses and reduction of germinal cell formation.[37] A randomized, placebo-controlled phase II study (NCT NCT02565576) in AChR- and MuSK ab positive generalized MG showed no significant improvement, but good safety.[55]

Since in MG T-cells induce B-cell proliferation and differentiation into plasma cells via cytokines, drugs inhibiting cytokines or T-cells may be another valuable treatment option in MG. T-cell directed treatment strategies include tocilizumab, an anti-IL-6 receptor ab binding to IL-6R and thereby inhibiting the inflammatory cascade. Tocilizumab was shown to have beneficial effects in some MG patients refractory to rituximab.[56] Satralizumab is a pharmacologically optimized IL6-R inhibitor with a prolonged half-time due to enhanced ab recycling. It is administered subcutaneously. Satralizumab binds membrane-bound or soluble IL-6R and has recently been approved for NMO spectrum disease on the basis of a phase III study.[57] A phase III study of satralizumab in AChR-ab positive MG is currently recruiting.[58] Brodalumab, an anti-IL-17/Il-17RA monoclonal ab which inhibits autoaggressive T- lymphocytes, represents another drug addressing the cytokine pathway and might be effective in MG.[6] Further candidates are secukinumab inhibiting the IL-17- and rontalizumab inhibiting the INF-alpha pathways and abatacept, a fusion protein consisting of the Fc part of IgG1 and the extracellular domain of human cytotoxic T-lymphocyte-associated antigen 4 (CTLA4), which can bind to CD 80- and CD 86-positive cells, thereby inhibiting co-stimulation of T cells by antigen-presenting cells.[6]

Chimeric antigen receptor (CAR)-T-cell therapy

Phase II trials on CD8 positive CAR-T-cell therapy directed against plasma cells that express the B-cell maturation antigen (BCMA) are underway in MG after this treatment strategy has been approved by the FDA for B-cell-acute lymphatic leukemia and B-cell lymphoma.[6,59] This treatment principle is regarded as especially promising for MuSK ab positive MG.[60]

Further treatment strategies

Several smaller series of refractory MG patients treated by hematopoetic stem cell transplantation have been reported. In one series, hematopoetic stem cell transplantation was reported to induce a remission in seven patients, and they could stop all immunosuppressive treatment after 8 months. They remained in stable remission at a median follow-up time of 40 months.[61]

With an increased focus on parenteral MG therapy, both intravenous and subcutaneous immunoglobulin treatment have emerged as potential options for chronic MG therapy.[62] Subcutaneous immunoglobulins were also shown to be effective in mild to moderate exacerbations of myasthenia gravis.[62,63] These are antibody-unspecific treatments. Antigen-specific immunoabsorption, removing only the antibodies against AChR or MuSK, is a modification of plasmapheresis.[9] It is clinically effective, but not superior to ordinary plasmapheresis.

Antibodies that selectively eliminate autoantibodies involved in human disease (seldegs) have been developed, are effective in experimental disease, but have not yet been tried for MG.[64] A phase 2 study on the antisense oligonucleotide monarsen against AChR abs in MG showed only modest improvement in the QMG score.[65] No further trials have followed.

In theory, influencing non-AChR and non-MuSK targets in the muscle could improve muscle strength in MG. Tirasemtiv activates the troponin complex and was reported to improve MG symptoms in a few patients.[66] CIC-1 chloride channels

in skeletal muscle influence muscle strength and can be modified pharmacologically.[67] The ultimate aim should be to find therapies that are immunologically specific for the disease to be treated or even specific for the disease in the individual patient to be treated. That would mean to inhibit totally the action of the pathogenic antibodies against epitopes on AChR, MuSK or LRP4, either directly or through interference with the antigen-specific T cells. Further insight into single B and T cells with RNA-sequencing and gene expression analysis may elucidate their association to MG in detail and guide individually directed therapies.[3] A further theoretical aim would be to be able to prevent MG by antigen-specific vaccination.

Discussion

The main aim of this review has been to give an overview on potential new drugs for MG and to elucidate their mechanism of action. With the introduction of new drugs the therapeutic options in MG have changed, particular for refractory MG. With the approval of new and expensive substances, cost-benefit questions become prominent, but also potential risks of new versus old drugs. New therapeutic strategies and guidelines need to be developed by relevant bodies and based on all available evidence. Patients' quality of life and burden of disease analyzed more intensively in the last years, should be key elements in such evaluations. For the newest drugs, key evidence is still lacking.

Conclusion

There is an increasing spectrum of new drugs addressing cellular and molecular targets in MG pathogenesis and representing potentially effective and more selective treatment strategies (shown in the Figure 1). Several important clinical studies evaluating these drugs have been conducted in the last few years or are ongoing or planned (see Table 1). Further characterization of function and pathogenicity of the abs in MG is necessary. Increasing knowledge on ab-mediated pathophysiological mechanisms will help to improve MG therapy and could lead to the development of more individualized antigen-directed treatment approaches in the future.

Author contributions

CSG: Basic idea, data collection, drafting the manuscript, the table and the figure.

NEG: Data collection, drafting the manuscript, and revising the table and the figure.

Conflict of interest statement

The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Christiane Schneider-Gold has received consulting or speaker's honoraria from Alexion Pharmaceuticals, Amicus Therapeutics, Argenx, Bayer Schering, Hormosan Pharma, Immunovant, Lupin Pharmaceuticals, Roche Pharma and TEVA. Nils Erik Gilhus has received consulting or speaker's honoraria from Alexion, Argenx, Immunovant, Janssen, Merck, Octapharma, Ra, Roche, and UCB.

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References

1. Mantegazza R and Antozzi C. When myasthenia gravis is deemed refractory: clinical signposts and treatment strategies. *Ther Adv Neurol Disord*. Epub ahead of print 18 January 2018. DOI: 10.1177/1756285617749134.
2. Schneider-Gold C, Hagenacker T, Melzer N, *et al.* Understanding the burden of refractory myasthenia gravis. *Ther Adv Neurol Disord*. Epub ahead of print 1 March 2019. DOI: 10.1177/1756286419832242.
3. Howard JF Jr, Utsugisawa K, Benatar M, *et al.* Safety and efficacy of eculizumab in anti-acetylcholine receptor antibody-positive refractory generalised myasthenia gravis (REGAIN): a phase 3, randomised, double-blind, placebo-controlled, multicentre study. *Lancet Neurol* 2017; 16: 976–986.
4. Li T, Zhang GQ, Li Y, *et al.* Efficacy and safety of different dosages of rituximab for refractory generalized AChR myasthenia gravis: a meta-analysis. *J Clin Neurosci* 2021; 85: 6–12.
5. Melzer N, Ruck T, Fuhr P, *et al.* Clinical features, pathogenesis, and treatment of myasthenia gravis: a supplement to the

Guidelines of the German Neurological Society. *J Neurol* 2016; 263: 1473–1494.

6. Menon D, Barnett C and Bril V. Novel treatments in myasthenia gravis. *Front Neurol* 2020; 11: 538. DOI: 10.3389/fneur.2020.00538.
7. Koneczny I and Herbst R. Myashenia gravis: pathogenic effects of autoantibodies on neuromuscular architecture. *Cells* 2019; 8: 671. DOI: 10.3390/cells8070671.
8. Takamori M. Myasthenia gravis: from the viewpoint of pathogenicity focusing on acetylcholine receptor clustering, trans-synaptic homeostatis and synaptic stability. *Front Mol Neurosci* 2020; 13: 86. DOI: 10.3389/fnmol.2020.00086.
9. Lazaridis K and Tzartos SJ. Myasthenia gravis: autoantiobody specificity and their role in MG management. *Frontiers Neurol* 2020; 11: 596981.
10. Gilhus NE, Tzartos S, Evoli A, *et al.* Myasthenia gravis. *Nat Rev Dis Primers* 2019; 5: 30. DOI: 10.1038/s41572-019-0079-y.
11. Koneczny I, Cossins J, Waters P, *et al.* MuSK myasthenia gravis IgG4 disrupts the interaction of LRP4 with MuSK but both IgG4 and IgG1-3 can disperse preformed agrin-independent AChR clusters. *PLoS ONE* 2013; 8: e80695. DOI: 10.1371/journal.pone.0080695.
12. Stathopoulos P, Kumar A, Van der Heiden JA, *et al.* Mechanisms underlying B cell immune dysregulation and autoantibody production in MuSK myasthenia gravis. *Ann N Y Acad Sci* 2018; 1412: 154–165. DOI: 10.1111/nyas.1353.
13. Higuchi O, Hamuro J, Motomura M, *et al.* Autoantibodies to low-density lipoprotein receptor-related protein 4 in myasthenia gravis. *Ann Neurol* 2011; 69: 418–422. DOI: 10.1002/ana.22312.
14. Leite MI, Jacob S, Viegas S, *et al.* IgG1 antibodies to acetylcholine receptors in 'seronegative' myasthenia gravis. *Brain* 2008; 131: 1940–1952.
15. Jacob S, Viegas S, Leite MI, *et al.* Presence and pathogenic relevance of antibodies to clustered acetylcholine receptor in ocular and generalized myasthenia gravis. *Arch Neurol* 2021; 99: 994–1001.
16. Hoffmann S, Harms L, Schuelke M, *et al.* Complement deposition at the neuromuscular junction in seronegative myasthenia gravis. *Acta Neuropathol* 2020; 139: 1119–1122.
17. Schneider-Gold C, Krenzer M, Klinker E, *et al.* Immunoadsorption versus plasma exchange versus combination for treatment of myasthenic deterioration. *Ther Adv Neurol Disord* 2016; 9: 297–303.
18. Clifford KM, Hobson-Webb LD, Benatar M, *et al.* Thymectomy may not be associated with clinical improvement in MuSK myasthenia gravis. *Muscle Nerve* 2019; 59: 404–410.
19. Wolfe GI, Kaminski HJ, Aban IB, *et al.* Randomized trial of thymectomy in myasthenia gravis. *N Engl J Med* 2016; 375: 511–522. DOI: 10.1056/NEJMoa160248.
20. Hehir MK, Hobson-Webb LD, Benatar M, *et al.* Rituximab as treatment for anti-MuSK myasthenia gravis: multicenter blinded prospective review. *Neurology* 2017; 89: 1069–1077.
21. Topakian R, Zimprich F, Iglseder Embacher N, *et al.* High efficacy of rituximab for myasthenia gravis: a comprehensive nationwide study in Austria. *J Neurol* 2019; 266: 699–706.
22. Nowak R, Coffey C, Goldstein J, *et al.* Rituximab in patients with moderate to severe myasthenia gravis: a subgroup analysis of the BeatMG study. *Muscle Nerve* 2019; 60: S139.
23. Brauner S, Eriksson-Dufva A, Hietala MA, *et al.* Comparison between rituximab treatment for new-onset generalized myasthenia gravis and refractory generalized myasthenia gravis. *JAMA Neurol* 2020; 77: 974–981.
24. Beecher G, Anderson D and Siddiqi ZA. Rituximab in refractory myasthenia gravis: extended prospective study results. *Muscle Nerve* 2018; 58: 452–455.
25. Dos Santos A, Noury JB, Genestet S, *et al.* Efficacy and safety of rituximab in myasthenia gravis: a French multicentre real-life study. *Eur J Neurol* 2020; 27: 2277–2285.
26. Gilhus NE. Myasthenia gravis. *N Engl J Med* 2016; 375: 2570–2581.
27. Choi K, Hong YH, Ahn SH, *et al.* Repeated low-dose rituximab treatment based on the assessment of circulating B cells in patients with refractory myasthenia gravis. *Ther Adv Neurol Disord*. Epub ahead of print 18 September 2019. DOI: 10.1177/1756286419871187.
28. Lu J, Zhong H, Jing S, *et al.* Low-dose rituximab every 6 months for the treatment of acetylcholine receptor-positive refractory myasthenia gravis. *Muscle Nerve* 2020; 61: 310–315. DOI: 10.1002/mus.26790.

29. BeatMG: Phase II trial of rituximab in myasthenia gravis, https://clinicaltrials.gov/ct2/show/NCT02110706
30. Tandan R, Hehir MK, Waheed W, *et al.* Rituximab treatment of myasthenia gravis: a systematic review. *Muscle Nerve* 2017; 56: 185–196.
31. Hehir MK, Hobson-Webb LD, Benatar M, *et al.* Rituximab as treatment for anti-MuSK positive myasthenia gravis: multicenter blinded prospective review. *Neurology* 2017; 89: 1069–1077.
32. Cree BAC, Bennett JL, Kim HJ, *et al.* Inebilizumab for the treatment of neuromyelitis optica spectrum disorder (N-MOmentum): a double-blind, randomised placebo-controlled phase 2/3 trial. *Lancet* 2019; 394: 1352–1363. DOI: 10.1016/S0140-6736(19) 31817-3.
33. Myasthenia gravis inebilizumab trial (MINT), https://clinicaltrials.gov/ct2/show/NCT04524273
34. Russell A, Yaraskavitch M, Fok D, *et al.* Obinutuzumab plus chlorambucil in a patient with severe myasthenia gravis and chronic lymphocytic leukemia. *J Neuromuscul Dis* 2017; 4: 251–257. DOI: 10.3233/JND-170211.
35. Lee DSW, Rojas OL and Gommermann JL. B cell depletion in autoimmune disease: advances and mechanistic insights. *Nat Rev Drug Discov* 2021; 20: 179–199.
36. US National Library of Medicine, ClinicalTrials.gov. A study of TACI (transmembrane activator and calcium-modulator and cyclophilin ligand (CAML) interactor): antibody fusion protein injection (RC18) in subjects with systemic myasthenia gravis, https://clinicaltrials.gov/ct2/show/NCT04302103
37. Alabbad S, AlGaeed M, Sikorski P, *et al.* Monoclonal antibody-based therapies for myasthenia gravis. *BioDrugs* 2020; 34: 557–566. DOI: 10.1007/s40259-020-00443-w.
38. Hewett K, Sanders DB, Grove RA, *et al.* Randomized study of adjunctive belimumab in participants with generalized myasthenia gravis. *Neurology* 2018; 90: e1425–e1434. DOI: 10.1212/WNL.0000000000005323.
39. Gomez AM, Wilcox N, Vrolix K, *et al.* Proteasome inhibition with bortezomib depletes plasma cells and specific autoantibody production in primary thymic cell cultures from early onset myasthenia gravis patients. *J Immunol* 2014; 193: 1055–1063.
40. Jin WL, Luo Z and Yang H. Peripheral B cell subsets in autoimmune diseases: clinical implications and effects of B cell-targeted therapies. *J Immunol Res* 2020; 2020: 9518137. DOI: 10.1155/2020/9518137.
41. Schneider-Gold C, Reinacher-Schick A, Ellrichmann G, *et al.* Bortezomib: first experience in severe MuSK-antibody positive myasthenia gravis. *Ther Adv Neurol Disord* 2017; 10: 339–341.
42. Therapy of antibody-mediated autoimmune diseases by Bortezomib (TAVAB), https://clinicaltrials.gov/ct2/show/NCT02102594
43. ClinicalTrials.gov. A phase 2, randomized, placebo-controlled study to evaluate safety, tolerability, and efficacy of TAK-079 in patients with generalized myasthenia gravis, https://clinicaltrials.gov/ct2/show/NCT04159805
44. Dalakas MC, Alexopoulos H and Spaeth PJ. Complement in neurological disorders and emerging complement-targeted therapeutics. *Nat Rev Neurol* 2020; 16: 601–617. DOI: 10.1038/s41582-020-0400-0.
45. Muppidi S, Utssugisawa K, Benatar M, *et al.* Long-term safety and efficacy of eculizumab in generalized myasthenia gravis. *Muscle Nerve* 2019; 60: 14–24.
46. US National Library of Medicine, ClinicalTrials.gov. Ravulizumab, 2020, https://clinicaltrials.gov/ct2/show/NCT03920293
47. Howard JF Jr, Nowak RJ, Wolfe GI, *et al.* Clinical effects of the self-administered subcutaneous complement inhibitor zilucoplan in patients with moderate to severe generalized myasthenia gravis: results of a phase 2 randomized, double-blind, placebo-controlled, multicenter clinical trial. *JAMA Neurol* 2020; 77: 582–592.
48. Dalakas MC and Spaeth PJ. The importance of FcRn in neuro-immunotherapies: from IgG catabolism, FCGRT gene polymorphisms, IVIg dosing and efficiency to specific FcRn inhibitors. *Ther Adv Neurol Disord*. Epub ahead of print 26 February 2021. DOI: 10.1177/1756286421997381.
49. Peter HH, Ochs HD, Cunningham-Rundles C, *et al.* Targeting FcRn for immunomodulation: benefits, risks, and practical considerations. *J Allergy Clin Immunol* 2020; 146: 479–491.
50. Howard JF Jr, Bril V, Vu T, *et al.* Safety, efficacy, and tolerability of efgartigimod in patients with generalised myasthenia gravis (ADAPT): a multicentre, randomised, placebo-controlled, phase 3 trial. *Lancet Neurol* 2021; 20: 526–536. DOI: 10.1016/S1474-4422(21)00159-9.
51. Evaluating the pharmacodynamic noninferiority of efgartigimod PH20 SC administered subcutaneously as compared to efgartigimod

administered intravenously in patients with generalized myasthenia gravis, https://clinicaltrials.gov/ct2/show/NCT04735432

52. Bril V, Benatar M, Andersen H, *et al.* Efficacy and safety of rozanolixizumab in moderate to severe generalized myasthenia gravis. A phase 2 randomized control trial. *Neurology* 2021; 96: e853–e856. DOI: 10.1212/WNl 000000000011108.

53. ClinicalTrials.gov. A study to evaluate the safety, tolerability, efficacy, pharmacokinetics and pharmacodynamics of M281 administered to adults with generalized myasthenia gravis, 2020, https://clinicaltrials.gov/ct2/show/NCT03772587

54. ClinicalTrials.gov. A study of RVT-1401 in myasthenia gravis (MG) patients, 2020, https://clinicaltrials.gov/ct2/show/NCT03863080

55. ClinicalTrials.gov. Safety, tolerability, pharmacokinetics and efficacy of CFZ533 in moderate to severe myasthenia gravis, 2019, https://clinicaltrials.gov/ct2/show/NCT02565576

56. Jonsson DI, Pirskanen R and Piehl F. Beneficial effect of tocilizumab in myasthenia gravis refractory to rituximab. *Neuromuscul Disord* 2017; 27: 565–568. DOI: 10.1016/j.nmd.2017.03.007.

57. Traboulsee A, Greenberg BM, Bennett JL, *et al.* Safety and efficacy of satralizumab monotherapy in neuromyelitis optica spectrum disorder: a randomised, double-blind, multicentre, placebo-controlled phase 3 trial. *Lancet Neurol* 2020; 19: 402–412. DOI: 10.1016/S1474-4422(20)30078-8.

58. A study to evaluate efficacy, safety, pharmacokinetics and pharmacodynamics of sartralizumab in generalized myasthenia gravis, https://clinicaltrials.gov/ct2/show/NCT04963270

59. Descartes-08 CAR-T cells in generalized myasthenia gravis (MG), https://clinicaltrials.gov/ct2/show/NCT04146051

60. Oh S, O'Connor K and Payne A. Muscle-specific tyrosine kinase chimeric autoantibody receptor T cells (MUSK-CAART) as a precision cellular immunotherapy for antigen-specific B cell depletion in MuSK myasthenia gravis (MG). *Muscle Nerve* 2020; 62: S116–S116.

61. Bryant A, Atkins H, Pringle CE, *et al.* Myasthenia gravis treated with autologous hematopoietic stem cell transplantation. *JAMA Neurol* 2016; 73: 652–8. DOI: 10.1001/jamaneurol.2016.0113.

62. Alcantara M, Sarpong E, Barnett C, *et al.* Chronic immunoglobulin maintenance therapy in myasthenia gravis. *Eur J Neurol* 2021; 28: 639–646.

63. Beecher G, Anderson D and Siddiqi ZA. Subcutaneous immunoglobulin in myasthenia gravis exacerbation. A prospective open-label trial. *Neurology* 2017; 89: 1135–1141.

64. Sun W, Khare P, Wang XL, *et al.* Selective depletion of antigen-specific antibodies for the treatment of demyelinating diseases. *Molecular Therapy* 2021; 29: 1312–1323.

65. Sussman JD, Argov Z, McKee D, *et al.* Antisense treatment for myasthenia gravis. *Ann N Y Acad Sci* 2008; 1132: 283–290. DOI: 10.1196/annals.1405.022.

66. Sanders DB, Rosenfeld J, Dimachkie MM, *et al.* A double-blinded, randomized, placebo-controlled trial to evaluate efficacy, safety and tolerability of single doses of tirasemtiv in patients with acetylcholine receptor binding antibody-positive myasthenia gravis. *Neurotherapeutics* 2015; 12: 455–460.

67. Altamura C, Desaphy JF, Conte D, *et al.* Skeletal muscle ClC-1 chloride channels in health and disease. *Pflugers Arch* 2020; 247: 961–975.