Neurological Sciences
https://doi.org/10.1007/s10072-021-05077-6

REVIEW ARTICLE

Benefit and danger from immunotherapy in myasthenia gravis

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Received: 19 November 2020 / Accepted: 18 January 2021

Abstract

In the last years, significant advances have improved the knowledge of myasthenia gravis (MG) immunopathogenesis and have enabled to realize new molecules with a selective action targeting compounds of the immunological system. This review discusses emerging treatments for MG, including complement inhibitors, neonatal Fc receptor targeting agents, and B cell interfering drugs, focusing on benefit and danger. In the second section of the review, several related adverse events of immunotherapy, including MGonset, are debated.

Keywords Refractory myasthenia gravis · Emerging therapy · Immunotherapy · Checkpoint inhibitors

Introduction

Myasthenia gravis (MG) is an autoimmune disease caused by autoantibodies targeting neuromuscular junction (NMJ) components as the acetylcholine receptor (AChR), muscle-specific kinase (MuSK), and lipoprotein-related peptide 4 (LRP4). Therapeutic strategies are intended to achieve an adequate control of disease minimizing the adverse events [1] and they include pyridostigmine, corticosteroids, and immunosuppressants (i.e., azathioprine, mycophenolate mofetil). Depletion or neutralization of serum autoantibodies by plasma exchange (PLEX) or intravenous immunoglobulins (IVIg) is useful in myasthenic crisis and disease exacerbations [1]. Long-term conventional immunosuppressants may be associated with the risk of intolerance, delayed onset of action, and systemic toxicity. One third of patients can be affected by "refractory MG" [2].

In the last years, significant advances have been reached in MG therapy. Improved knowledge of MG immunopathogenesis has enabled to realize new molecules, some of them already used in other autoimmune and neoplastic diseases, targeting compounds of the immunological system as B cells, pro-inflammatory cytokines, and their receptors, complement system, and Fc neonatal receptor (FcRn) [3–7]. Moreover, several biological targeting therapies for other immune-related disorders have been associated with the worsening or the onset of MG [8–10]. Most recently, immunotherapy for cancer by checkpoint inhibitors, which break off the immune system blocking cytotoxic T lymphocyte-associated protein 4 (CTLA-4) and programmed cell death protein 1 (PD-1) binding to their receptors, has been associated with several immune-related adverse events including MG onset [11]. The present review is focused on the benefit and danger of the emerging therapy for MG and on possible related effects caused by immunotherapy.

Complement inhibitors

Considering that complement cascade has an important role in MG pathogenesis linked to IgG1 antibodies (Abs) against AChR, the benefit of complement inhibitors in MG treatment has been proved [12]. *Eculizumab* is a humanized recombinant monoclonal antibody that, binding to C5 fragment, prevents its cleavage, formation of complement terminal complex [membrane attack complex (MAC)], and subsequent NMJ damage [13]. The US Food and Drug Administration (FDA)

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Published online: 05 February 2021

approved eculizumab for the treatment of paroxysmal nocturnal hemoglobinuria [PNH] (2007), atypical hemolytic uremic syndrome [aHUS] (2011), neuromyelitis optica spectrum disorder [NMOSD] (2020) [3–5], and AChR Abs+ generalized MG (gMG) [14].

It was also approved for refractory AChR Abs + gMG in Europe [15]. Efficacy, safety, and tolerability had been clearly proved in phase 3 (REGAIN study, induction dose of 900 mg/week for 4 doses followed by a maintenance dose of 1200 mg at week 4 and then every 2 weeks) and in an open-label extension (OLE study, a dose of 1200 mg at week 4, and then every 2 weeks) clinical trials [16, 17].

Neisseria meningitides vaccination at least 2 weeks prior to the first dose of eculizumab is required [16, 17]. Other adverse events include headache and nasopharyngitis [16, 17]. *Ravulizumab* is an intravenous humanized monoclonal Ab high-affinity C5 inhibitor, with a half-life longer than eculizumab. FDA-approved ravulizumab for PNH and aHUS treatment after clinical trials in which it was effective like eculizumab but with a reduced frequency of administration (every 8 weeks instead of 2 weeks) [18]. A phase 3 clinical trial in refractory MG is ongoing. *Zilucoplan* is a small peptide that blocks the cleavage of C5. A randomized, double-blind, placebo-controlled, phase 2 study was conducted in 44 patients affected by AChR Ab+ gMG to evaluate subcutaneous (SC) zilucoplan clinical effect [19]. The patients treated with zilucoplan 0.3 mg/kg daily for 12 weeks showed a statistically significant improvement in primary and secondary endpoints compared with the placebo group. Zilucoplan showed a favorable safety profile with minor side effects and without meningococcal infection. The phase 3 study to confirm the safety and efficacy of zilucoplan in gMG is ongoing.

Neonatal fc receptor antagonists

FcRn, expressed on endothelial cells, prolongs half-life of serum albumin and IgG by their recycling. IgG and albumin are bound by FcRn with a high affinity at endosomal acidic pH (5.0–6.5). Then, avoiding lysosomal degradation, they are released across a cellular surface at neutral pH of 7.4 [20]. FcRn inhibitors reduce IgG plasma levels, blocking their recycling and increasing their clearance. FcRn inhibition could be a promising therapeutic option in AChR Ab+ and MuSK Ab+ MG.

Efgartigimod is an engineering human IgG1-derived Fc fragment. Considering the similar FcRn-binding features of human and cynomolgus monkey IgG, the effect of efgartigimod on serum levels IgG-depleting was found in this animal species and in human healthy volunteers [21]. In phase 2, randomized at ratio 1:1, trial on 24 AChR Ab+ gMG patients, a rapid and sustained decrease of IgG (70.7%) and AChR Ab serum levels (40–70%) was seen in the efgartigimod group compared with the placebo group. Simultaneously, a significant clinical improvement emerged in quantitative myasthenia gravis (QMG), Myasthenia gravis activities of daily living profile (MG-ADL), Myasthenia Gravis Composite (MGC), and Myasthenia Gravis Quality of Life 15-item (MG-QoL15r) scales [22]. Efgartigimod was well tolerated. The most frequent treatment-emergent adverse events (TEAEs) were headache and reduction of monocyte count [22]. A phase 3 clinical trial is currently underway [23].

Rozanolixizumab is a high affinity humanized monoclonal IgG4P Ab direct against FcRn taking the advantage of SC administration. In phase 2, placebo-controlled study, 43 severe AChR Ab+ and MuSK Ab+ gMG patients were randomized to receive SC 7 mg/kg rozanolixizumab or placebo, and after 4 weeks, they were re-randomized to 3 weekly doses of either 4 or 7 mg/kg [24]. The QMG, MG-ADL, and MGC responder rates were 38.1%, 47.6%, and 47.6%, respectively, for the rozanolixizumab group compared to 22.7%, 13.6%, and 27.3%, respectively, for the placebo group. IgG and AChR Ab+ titers decreased by 68% from baseline 24. Headache was the most common side effect. A phase 3 study is ongoing.

Nipocalimab (M281) is a human de-glycosylated IgG1 monoclonal antibody with a high affinity to FcRn. In a phase 1 study, 50 healthy volunteers were organized in SAD (single ascending doses) cohort (n=34), treated with doses of 0.3–3–10–30–60 mg/kg (24 with M281, 10 with placebo), and MAD (multiple-ascending doses) cohort (n=16) receiving 4 weekly 15 mg/kg (n=6) or 30 mg/kg (n=6) of M281 or placebo (n=4) [25]. IgG serum reduction was M281 dose-dependent. During SAD, 74% and 80% decrease in IgG titers was observed at doses of 30 and 60 mg/kg, respectively, in MAD cohort up to ≈85%. No serious TEAEs and a low rate of infection were reported in the M281 group. Antidrug Abs were low in SAD (12%) and in MAD (31%) patients [25]. A phase 2 study to evaluate the safety, tolerability, and efficacy of M281 was completed in June 2020. Sixty patients with AChR+ or MuSK+ gMG were organized into 5 arms of treatment (4 with IV M281 and 1 IV placebo), and the results are still not available [26].

B cell targeting agents

B cells are the principal components of the humoral immune response. They are crucial in MG immunopathogenesis by the generation of autoantibodies and by a presentation of antigens on their surface with class II major histocompatibility complex (MHCII) inducing T cells to secrete proinflammatory cytokines [27]. B cell-activating factor (BAFF) is a factor which, binding its receptor on B cell surface, blocks apoptosis and induces proliferation and differentiation of B lymphocytes into plasma cells [28]. CD20 antigens are phosphoproteins

expressed on B cell surface involving in their activation and differentiation. Monoclonal Abs direct against CD20 proteins can induce B lymphocytes depletion by their direct apoptosis or complement-dependent cytolysis or antibody-dependent cell-mediated cytotoxicity [29]. B lymphocyte depletors can act directly or indirectly.

Direct B cells targeting agents

Rituximab (RTX) is a chimeric human/mouse IgG1 monoclonal Ab acting against CD20 approved by the FDA for rheumatoid arthritis [RA], non-Hodgkin lymphoma, chronic lymphocytic leukemia, pemphigus vulgaris, granulomatosis with polyangiitis, and microscopic polyangiitis [30], and it is in off-label prescription for refractory systemic lupus erythematosus (SLE) [6]. Data currently available show RTX effectiveness and tolerability in AChR Ab+ refractory MG, especially in MuSK Ab+ (regime more used: 375mg/m^2/week four consecutive weeks and 1000 mg on day 1 and day 15). The greatest response of RTX in MuSK Ab + patients could be explained by the major effect of the drug on IgG4-producing B cells [31, 32]. A review comparing 169 patients (59% AChR-Ab+, 34% MuSK-Ab+) showed that modified MGFA (Myasthenia Gravis Foundation of America) post-intervention scale of minimal manifestations (MM) or better occurred in 72% of MuSK Ab+ MG patients and in 30% of AChR Ab + MG patients and that post-treatment relapses were less frequent in MuSK Ab+ MG [33]. In a systematic review, 165 AChR Ab+ MG patients from 13 studies were analyzed to evaluate the best evidence for RTX in subtype AChR Ab+ MG [34]. Clinical improvement after treatment was reported in 68% of patients, and a reduction of the immunosuppressant average dose was obtained in 9 studies [34]. A recent review showed better outcomes in gMG patients treated with RTX in the early phase of disease compared with those treated 12 or more months from disease onset, and a shorter time of remission in the RTX group than in the conventional immunosuppressant group [35]. Therefore, they speculated that RTX should be considered a recommended therapy in new-onset disease. Some studies were conducted to evaluate the efficacy and safety of repeated low-dose RTX in patients with refractory MG that could be a cost-effective therapeutic option [36].

In contrast to promising data obtained from retrospective studies, in phase 2, randomized, placebo-controlled trial (BeatMG study) not statistically significant difference was found between RTX and placebo group considering corticosteroid-sparing as the primary outcome [37]. A phase 3 trial is ongoing. To date, rituximab is usually well tolerated and it can be considered a worthwhile option to treat MuSK+ Ab-related gMG [38]. In a few cases, side effects were reported, including flushing, allergic reaction, headache, fever, myocardial infarction, diabetes, and hypertension [33, 34, 38]. Immunosuppression and agranulocytosis due to B cell depletion occasionally lead to infections and to reactivation of herpes zoster [33, 34]. The risk of RTX-induced progressive multifocal leukoencephalopathy (PML) should not underestimated and serum determination of anti-John Cunningham virus (JCV) Abs is required prior to treatment. One case of PML-induced death has been reported [39].

Ofatumumab, obinutuzumab, and ocrelizumab are other anti-CD20 agents representing potential future therapeutic alternatives for refractory MG [40–42].

Indirect B cells targeting agents

Belimumab is a human IgG1λ monoclonal Ab against B lymphocyte stimulator (BLys) against BAFF and approved for SLE treatment [43]. Some studies showed that serum BAFF levels in MG patients (especially AChR Ab+) were higher than those of controls. BAFF seems to have a role in MG pathogenesis and, therefore, to be a potential novel therapeutic target [44]. In phase 2, randomized, placebo-controlled clinical trial, not statistically significant difference was found between belimumab and placebo group in primary efficacy endpoint (QMG score) at 24 weeks [45]. The most frequent TEAEs, in belimumab (78%) and placebo (91%) groups, were flu and nausea, headache, diarrhea, and back pain [45].

Bortezomib is a dipeptide that, inhibiting proteasome function, induces accumulation of misfolded or unfolded proteins in plasma cells culminating in cell death. Bortezomib, used in multiple myeloma and "mantle cell lymphoma" treatment [7], seems to be a new therapeutic approach in autoimmune diseases [46]. Promising results were achieved in a single case of severe refractory MuSK Ab + MG [47]. A phase 2 study was conducted on refractory MG, SLE, and RA patients to evaluate proteasome-inhibitor capacity to improve the clinical course of autoimmune diseases decreasing serum autoantibody [48]. Sensorimotor polyneuropathy and reactivation of herpes virus infection may be a risk (30–40% of treated cases) for patients taking bortezomib due to its neurotoxicity [49]. *Etanercept* (human soluble anti-TNF fusion protein), *Infliximab* (chimeric human-mouse Ab), and *Adalimumab* (humanized anti-TNF Ab) are TNF (tumor necrosis factor)-inhibitors (TNFis) that prevent the interaction of TNFα and TNF ß with cell-surface TNF receptors. TNF is a proinflammatory cytokine that plays a critical role in the pathogenesis of autoimmune diseases. Studies showed that TNF is involved in the activation of AChR-specific T and B cells in EAMG [50]. Anti-TNF agents downregulate TNF-induced inflammatory response and cause TNFα-secreting cells lysis.

They are approved for autoimmune disease treatment such as RA. Contrasting data have been reported in the literature concerning the benefit of these drugs in MG. During long-term TNFis treatment, the risk of infection and autoimmune phenomena should not be underestimated. In a pilot study, etanercept was effective in 8/11 MG corticosteroid-

dependent patients with a low-serum level of IL-6 (interleukin-6) and IFN-γ (interferon-γ). 2/11 patients with a higher level of abovementioned cytokines presented MG symptoms worsening [8]. Individual cases of MG onset/exacerbation during concomitant treatment with anti-TNF agents have been described [9, 10]. Therefore, careful monitoring of the treatment is required, and further immunological studies are needed to verify the TNFis safety. A valid potential therapeutic approach in MG is based on proinflammatory cytokine activity inhibition. IL-6, generated by different cells, including monocytes and B cells, induces the switching from suppressive regulatory T cells (Treg) to pathogenic T helper 17 (Th17) cells and promotes B cell differentiation into antibody-secreting cells. Equilibrium between Treg and Th17 cells is perturbed in EAMG upregulating Th17 subtype [51]. Blockade of IL-6 in EAMG murine model reduced B cells and anti-AChR Ab levels [51].

Tocilizumab, a recombinant humanized anti-IL6 receptor Ab, was approved for RA, Castelman's disease and juvenile idiopathic arthritis treatment, and it was beneficial in two cases of MG severe and refractory to rituximab [52]. No TEAEs were reported; however, perforated diverticulitis occurred in patients with RA receiving the drug [53]. Tocilizumab has been used in severe cases of COVID-19: one patient with MG, receiving tocilizumab after a myasthenic crisis, was extubated without myasthenic exacerbation [54]. As a result, tocilizumab may be considered a suitable alternative of therapy in refractory MG, especially in those cases overlapping with COVID-19 disease. Clinical trials are necessary to evaluate the effectiveness and safety of this drug. A summary of emerging MG therapy characteristics is reported below in Table 1.

The other side of immunotherapy

MG can be worsened or, more often triggered, by medications acting at different levels on the immune system. In these cases, toxicity is not MG-specific, as these agents may be associated with a variety of immune-related adverse events (irAEs), MG is mostly associated with anti-AChR Abs and, typically, patients develop MG within weeks or months after treatment and may recover after treatment withdrawal. Up to 7% of patients treated with d-penicillamine develop MG, mostly with mild generalized or purely ocular manifestations. The effect on the immune system is not clear, but the observation that MG occurs more commonly during d-penicillamine treatment for rheumatoid arthritis than for Wilson's disease suggests that a genetic background predisposing to autoimmunity may play a role [55].

MG onset or worsening has been reported during treatment with INF-α in at least 40 patients. Such a complication was more common among subjected treated for chronic C hepatitis than in those with cancer. MG occurred in 4 patients receiving INF-β, mostly during treatment for multiple sclerosis [56]. The use of TNFis has been associated with a number of irAEs, mainly cutaneous vasculitis, lupus-like syndrome, SLE, and interstitial lung disease. Autoimmunity may be induced by a cytokine shift, as TNFis suppresses T helper Th1 responses and favors Th2 cells and type I interferons [57]. Development of MG has been associated with etanercept [58], adalimumab [10], and etanercept plus ustekinumab (anti-interleukin12/23) [9]. In a pilot trial on etanercept in steroid-dependent MG pts, 8 of 11 patients completed the study and two were withdrawn due to a severe MG worsening [8].

In recent years, cancer treatment with immune checkpoint inhibitors has gained widespread interest given its potential to induce a variety of irAEs, including MG. The mechanisms underlying these unwanted effects and the characteristics of the associated disease will be discussed in more detail.

Immune checkpoint inhibitors and associated irAEs

Immune checkpoints (ICPs) are inhibitory molecules, expressed on T cell surface, that modulate the immune system, maintaining self-tolerance and preventing host tissue damage by uncontrolled responses to foreign or self-antigens. Through overexpression of ICPs, cancer cells elude T cell-mediated destruction. CTLA-4 and PD-1 are the best characterized ICPs and the main target of cancer immunotherapy. CTLA-4 is a homolog of CD28 (the costimulatory receptor on T cells) that binds CD80 and CD86 on dendritic cells with higher affinity than CD28, substantially reducing T cell activation [59, 60] (Fig. 1a). CTLA-4 is constitutively expressed on T-regulatory (Treg) cells which play a crucial role in immune homeostasis [60].

PD-1 is expressed on activated T and B cells, natural killer cells, antigen-presenting cells, myeloid cells, and intratumoral Tregs [61]. Two PD-1 ligands have been identified (PD-L1 and -L2); of these, PD-L1 is expressed not only on immune cells, but also on epithelial cells and cancer cells [60]. Upon ligation, PD-1 acts downstream of T cell receptor reducing the expression of cytokines and transcription factors required for T cell function [59] (Fig. 1c). It is worth noticing that, while PD-1 is expressed on activated T cells in peripheral tissues, CTLA-4 exerts its effects on T lymphocytes primed in lymphnodes irrespective of the antigen specificity [59]. An additional mechanism of T cell immunosuppression is represented by the presence of activated FoXP3+Tregs within the lymphoid organs and the tumor microenvironment (Fig. 1e).

ICP inhibitors (ICI) are humanized monoclonal Abs targeting CTLA-4 (*nivolumab*), PD-1 (*nivolumab*, *pembrolizumab*) and PD-L1 (*tremelizumab, atezolizumab, avelumab, durvalumab*). Initially approved for melanoma, non-small cell lung carcinoma, and renal cell carcinoma, these agents have lately become available for a broad range of tumors and have dramatically changed the long-term prognosis

Table 1 Characteristics of emerging drugs for MG

Drug	Target	Mechanism of action	Administration	Mg study status	Main side effects
Eculizumab	C5	C5 inhibition	IV	Approved (USA, Europe, Japan)	Infection by encapsulated bacteria, headache, nasopharyngitis
Ravulizumab	C5	High-affinity C5 inhibition	IV	Phase III clinical trial ongoing	Similar to eculizumab
Zilucoplan	C5	C5 inhibition	SC	Phase III clinical trial ongoing	Potential risk of infection by encapsulated bacteria
Efgartigimod	FcRn	Prevention of FcRn-mediated IgG recycling	IV	Phase III clinical trial ongoing	Headache, reduction of monocyte count
Rozanolixizumab	FcRn	Prevention of FcRn-mediated IgG recycling	SC	Phase III clinical trial ongoing	Headache
Nipocalimab (M281)	FcRn	Prevention of FcRn-mediated IgG recycling	IV	Phase II clinical trial completed, results not published	Potential risk of infection
Rituximab	CD-20 B cells	B cells depletion	IV	Phase III clinical trial ongoing	Infections, allergic infusion reaction, reactivation of herpes zoster, PML
Belimumab	BAFF factor	Prevention of B cells differentiation into antibody-secreting cells	IV	Phase II clinical trial completed	Flu, nausea, one case of sepsis-induced death
Bortezomib	Proteasome	Plasma cells apoptosis by inhibition of proteasome	SC	Phase II clinical trial completed	Sensorimotor polyneuropathy
Etanercept	TNFα	TNFα inhibition	SC	No	Infection and autoimmune phenomena (including MG onset/worsening)
Infliximab	TNFα	TNFα inhibition	IV	No	Similar to etanercept
Adalimumab	TNFα	TNFα inhibition	SC	No	Similar to etanercept
Tocilizumab	IL-6 receptor	Blocking of a switch from suppressive Treg to pathogenic Th17 cells	IV	No	Good safety

MG myasthenia gravis, *C5* fragment 5 of complement, *IV* intravenous, *SC* subcutaneous, *FcRn* neonatal fragment crystallizable receptor, *IgG* immunoglobulin type G, *PML* progressive multifocal leukoencephalopathy, *BAFF* B cell-activating factor, *TNF* tumor necrosis factor, IL-6 interleukin-6, *Treg cells* suppressive regulatory T cells, *Th17 cells* T helper 17 cells

of metastatic cancer. Clinical effects rely on their ability to overcome the ICP overexpression in/around tumor tissue, allowing an effective anti-tumor response (Fig. 1b, d, f). Not surprisingly, unleashing the immune system occurs at the expense of tolerance breakdown [60]. Moreover, considering the ICP major targets, it is not surprising that irAEs occur more frequently with anti-CTLA-4 than with anti-PD-1/-PD-L1 treatment [62] and their frequency is higher (around 90%) in patients receiving ICI combination therapy [62].

Frequent irAEs are dermatologic, intestinal, hepatic, and endocrine diseases of mild to moderate severity (CTCAE - Common Terminology Criteria for Adverse Events grades 1–2). The only neurologic disorder in this group is sensorimotor neuropathy. Severe or life-threatening organ-specific irAEs, as cardiac, hematologic, rheumatic, and respiratory diseases, of any CTCAE grade, are classified as rare or infrequent. Neurological irAEs, including MG, are part of this group [63]. In a review including 9208 patients exposed to ICI treatment, the rate of any grade neurological irAEs was 3.8% with anti-CTLA4 mAbs, 6.1% for anti-PD1, and 12% with combination therapy. Most of these consisted of mild unspecific symptoms, like headache, dysgeusia, and dizziness. High-grade irAEs had an incidence below 1% for all types of treatment [64].

MG complicating treatment with immune checkpoint inhibitors

MG triggered by ICI treatment was first described in 2015 in two patients treated with ipilimumab for metastatic melanoma [65]. In subsequent studies, MG was found to be a rare, but a potentially fatal complication, with an estimated frequency, among patients treated with PD-1 inhibitors, ranging from 0.12–0.2% [66, 67]. Around 75% of these patients were positive for AChR Abs. A single patient with MuSK Abs has been reported so far [11]. From our literature review, de novo MG during ICI treatment was diagnosed so far in 9 patients treated with anti-CTLA-4, in 50 receiving PD1 or PD1-L inhibitors and in 9 under combined therapy. MG exacerbation

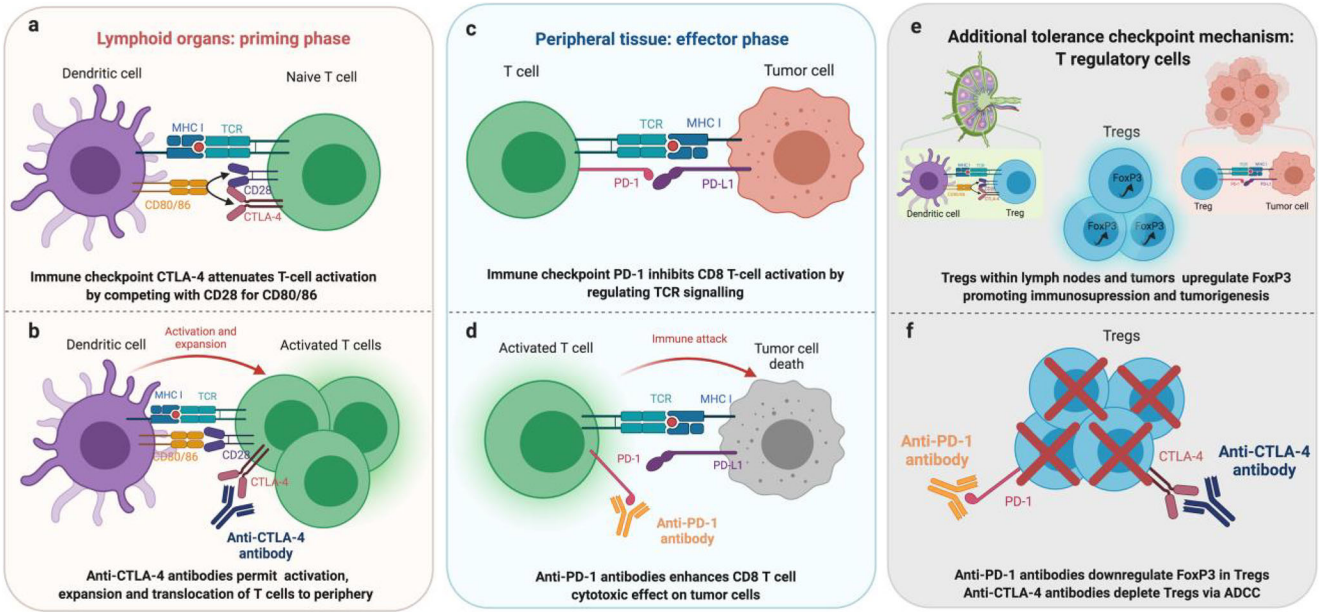

Fig. 1 Mechanism of CTLA-4 T cell inhibition during priming in secondary and tertiary lymph nodes (**a**). CTLA-4 blockade enhances CD28 co-stimulation and thus T cell activation (**b**). PD-1 is expressed by tissue-resident CD8 T lymphocytes and modulate TCR favoring their exhaustion (**c**). PD-1 blockade reverses exhaustion signals by blocking PD-1-PD-L1 interactions (**d**). Within the lymphoid organs and the tumor microenvironment, Tregs are activated and upregulate FoxP3 expression (**e**). Treg depletion caused by anti-CTLA-4 and anti-PD-1 mAbs is due to ADCC and Treg survival reduction, respectively (**f**). The figure was done using Biorender.com. ADCC antibody-dependent cellular cytotoxicity, CTLA-4 cytotoxic T lymphocyte antigen 4, FoxP3 forkhead, box P3; mAbs monoclonal antibodies, PD-1 programmed death cell protein 1, TCR T cell receptor, Tregs T regulatory cells

by anti-PD-1 was reported in 12 cases. These data are shown in Fig. 2a.

In 51% of patients, MG was the only irAE reported. Otherwise, it was frequently associated with myositis (particularly necrotizing myopathy, but also polymyositis, dermatomyositis, and unspecific myopathy), and, less commonly, with myocarditis or a combination of myositis and myocarditis. In a low proportion of cases, all these diseases were concomitant with polyneuropathy. Figure 2b illustrates these findings.

The co-occurrence of MG and myositis, with or without myocarditis, is rare and, apart from ICI-treated patients, had been reported mostly in patients with thymoma [68, 69]. Recently, treatment with ICP inhibitors has been proposed for advanced thymoma and thymic carcinoma and is currently being evaluated in phase 2 trials. However, all these diseases as severe or fatal irAEs were reported during anti-PD1 treatment in these cases [70, 71]. MG onset or deterioration generally occurred in the early phase of ICI treatment. Symptom severity was variable, with around 10% of cases with ocular or mild generalized MG and the great majority of patients rapidly progressing to moderate-severe symptoms [11, 72].

Mortality is around 25–30%, mostly due to MG crises, although myocarditis, when associated, is frequently fatal. Therefore, early diagnosis, close clinical monitoring, and prompt treatment are crucial. Most patients improved with aggressive treatment that included high-dose steroids, PLEX, or IVIg [11, 63, 73]. Rituximab can be used in patients unresponsive to first-line therapy [63].

In most cases, ICI treatment was discontinued after MG onset. Re-challenge with ICIs had mixed outcomes with some patients experiencing recurrent irAEs and others tolerating treatment without complications [72].

Conclusion

In the last decade, the need for more effective treatments, led to an increased use of biologics and to the development of more targeted therapies. RTX is a valid strategy in the therapy of MuSK Abs+ MG patients, and it could be suggested as a steroid-sparing agent in this form. Its effect is still unclear in AChR Abs + MG. Complement inhibitors, considering their greater targeting action, may represent one of the largest steps towards in immunotherapy. Eculizumab and ravulizumab can represent an approach to treat AChR-related refractory MG. FcRn inhibitors could be considered in short-term immunotherapy overcoming the limitations of PLEX and IVIg, including short duration of efficacy, repetitive doses, and a large volume of infusion.

Considering that FcRn inhibitors can induce a prolonged IgG depletion, they are a promising candidate for a first-line in

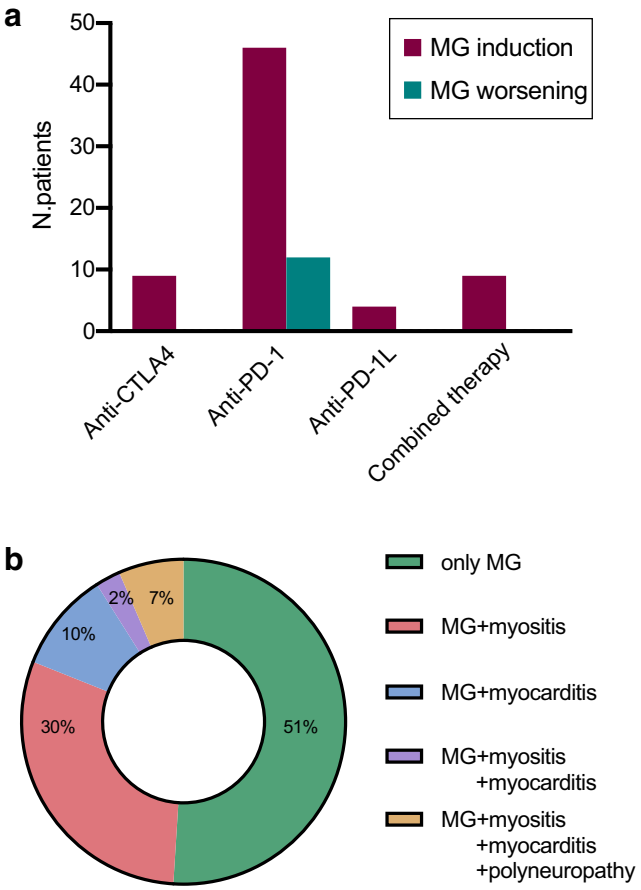

Fig. 2 **a, b** Seventy-nine cases of ICI- related MG have been described so far (**a**). The majority of these cases (85%) are triggered by ICI and, in particular, by anti-PD-1 drugs (62%). Half of the ICI-related MG cases has been described in association with another immune-mediated disease (**b**). ICI immune-checkpoint inhibitors, MG myasthenia gravis, PD-1 programming death 1. **2a.** Frequency of MG during ICI treatment with different agents. MG and associated diseases during ICI treatment

long-term immunosuppression therapy. Nevertheless, high cost, potential adverse events during chronic therapy, and production of anti-drug antibodies, represent some limitations of these new biologics. The future purpose is to discover unknown long-term effects of these drugs and to identify biomarkers of severity of disease to predict therapeutic response.

These advances fostered research work on the disease pathophysiology, on the mechanisms involved in the breakdown of immune tolerance. At the same time, from a better understanding of the immune tolerance, checkpoints stemmed the very effective cancer immunotherapy. As expected, the unlash of the immune system resulted in autoimmune adverse events. Clinicians must be aware of possible complications related to the use of biologics, and counterbalance benefits and dangers in individual patients.

Author's contributions All authors contributed equally to the paper.

Funding No funding was received for conducting this study.

Declarations

Conflict of interest The authors have no relevant financial or non-financial interests to disclose.

Ethical approval None.

Informed consent None.

Abbreviations *MG,* Myasthenia gravis; *NMJ,* Neuromuscular junction; *gMG,* Generalized myasthenia gravis; *AChR,* Acetylcholine receptor; *MuSK,* Muscle-specific kinase; *LRP4,* Lipoprotein-related peptide 4; *PLEX,* Plasma exchange; *IVIg,* Intravenous immunoglobulins; *FcRn,* Fc neonatal receptor; *CTLA-4,* Cytotoxic T lymphocyte-associated protein 4; *PD-1,* Programmed cell death protein 1; *Ab,* Antibody; *MAC,* Membrane attack complex; *FDA,* US Food and Drug Administration; *PNH,* Paroxysmal nocturnal hemoglobinuria; *aHUS,* Atypical hemolytic uremic syndrome; *NMOSD,* Neuromyelitis optica spectrum disorder; *MGFA,* Myasthenia Gravis Foundation of America; *QMG,* Quantitative myasthenia gravis score; *SC,* Subcutaneous; *MG-ADL,* Myasthenia gravis activities of daily living profile; *QMG,* Myasthenia Gravis Composite; *MG-QoL15r,* Myasthenia Gravis Quality of Life 15-item; *TEAEs,* Treatment-emergent adverse events; *SAD,* Single ascending dose; *MAD,* Multiple ascending doses; *MHC,* Major histocompatibility complex; *BAFF,* B cell-activating factor; *RTX,* Rituximab; *RA,* Rheumatoid arthritis; *SLE,* Systemic lupus erythematosus; *JCV,* John Cunningham virus; *BLys,* B Lymphocyte stimulator; *EAMG,* Experimental autoimmune MG; *TNF,* Tumor necrosis factor; *IL-6,* Interleukin; *IFN,* Interferon; *TNFis,* TNF inhibitors; *Treg,* Suppressive regulatory T cells; *Th17,* T helper 17; *irAEs,* Immune-related adverse events; *ICPs,* Immune checkpoints; *ICI,* Immune checkpoints inhibitors; *CTCAE,* Common Terminology Criteria for Adverse Events

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