

## Review article: Understanding the burden of refractory myasthenia gravis

### Supplementary file

**Supplementary Table 1.** Definitions of refractory MG reported in publications cited in the review article.

Reference	Definition of refractory MG	Classification of definition <sup>a</sup>	Comment
Afanasiev <i>et al.</i> 2017 <sup>1</sup>	Severe MG symptoms (MGFA class IV or V) despite optimal use of prednisone and $\geq 1$ immunosuppressant for $\geq 6$ months; or past history of severe MG symptoms and now stabilized (MGFA class I–III) at the price of chronic treatment with IVIg and/or PE with regular programmed hospitalizations or with prednisone and immunosuppressants but with side effects necessitating their withdrawal	1,2,3	Monocentric retrospective study ( $n = 28$ )
Ando <i>et al.</i> 2015 <sup>2</sup>	Unstable MG defined as fluctuating MG that limits activities of daily life occasionally due to muscle weakness or fatigue, or deteriorated MG symptoms after medical treatment when compared with pretreatment symptoms (in comparison with stable MG: controlled or ameliorated preoperative symptoms when compared with pretreatment symptoms)	1	Unstable $n = 8$ ; stable $n = 47$
Baek <i>et al.</i> 2007 <sup>3</sup>	MuSK-positive generalized MG, refractory to steroids, IVIg, immunosuppressants, thymectomy, and less responsive to plasmapheresis	1	Case study
Barnett <i>et al.</i> 2013 <sup>4</sup>	Patients with moderate to severe MG and worsening symptoms who require IVIg or PE	2	Small study ( $n = 62$ )
Beecher <i>et al.</i> 2018 <sup>5</sup>	Suboptimal response (unchanged or worsening clinical status) to $\geq 2$ immunosuppressive therapies; inability to tolerate side effects related to multiple immunosuppressive therapies; inability to reduce steroid dose without relapse; or requirement for maintenance IVIg infusions or PE	1,2,3	Small prospective open-label study ( $n = 22$ )

Reference	Definition of refractory MG	Classification of definition <sup>a</sup>	Comment
Blaaha <i>et al.</i> 2010 <sup>6</sup>	Severe condition despite thymectomy and drug therapy (including corticosteroids, immunosuppressive drugs, and repeated doses of immunoglobulins)	1	Small study ( $n = 6$ )
Bourque <i>et al.</i> 2016 <sup>7</sup>	Patients with no prior use of IVIg but refractory to conventional oral therapies	1	Case series ( $n = 3$ )
Buzzard <i>et al.</i> 2015 <sup>8</sup>	Resistance, toxicities, or contraindications to conventional immunosuppressive treatments, and/or dependence on PE or IVIg	1,2,3,4	Case series ( $n = 6$ )
Cereda <i>et al.</i> 2009 <sup>9</sup>	Refractory course with increasingly frequent exacerbations that progressively require increasing doses of immunosuppressant (corticosteroids followed by azathioprine), frequent visits for plasmapheresis (in the case of a myasthenic crisis, approximately every 3 months), and regular use of IVIg (once per month)	5	Case history
Collongues <i>et al.</i> 2012 <sup>10</sup>	Failure to respond to thymectomy and $\geq 2$ immunosuppressive drugs, including steroids	1	Retrospective multicenter study (refractory MG, $n = 13$ ; nonrefractory MG, $n = 7$ )
Engel-Nitz <i>et al.</i> 2018 <sup>11</sup>	Patients with past or current use of $\geq 3$ immunosuppressive therapies (azathioprine, ciclosporin, MMF, oral corticosteroids, or methotrexate) within a 24-month period; or $\geq 1$ of the above immunosuppressive therapies plus $\geq 1$ therapy typically reserved for MG resistant to conventional therapies (i.e. cyclophosphamide, rituximab); or regular treatment with PE, defined as $\geq 6$ claims for treatment on separate dates within a 12-month period. Owing to the inability to distinguish IVIg used as a maintenance treatment from IVIg used as a fast-acting 'bridge' therapy, it was not included in the definition for refractory MG	1,2	Retrospective analysis of medical and pharmacy claims data (refractory MG, $n = 403$ ; nonrefractory MG, $n = 3811$ )
Evoli <i>et al.</i> 2003 <sup>12</sup>	Withdrawal of oral pyridostigmine owing to muscle cramps and excessive salivation; poor tolerance of azathioprine; severe generalized bulbar weakness	1,3	Case series ( $n = 13$ )

Reference	Definition of refractory MG	Classification of definition <sup>a</sup>	Comment
Gladstone <i>et al.</i> 2004 <sup>13</sup>	Symptoms of double vision, dysphonia, and dysphagia despite treatment with steroids, plasmapheresis, IVIg, azathioprine, and pyridostigmine	1	Case series ( <i>n</i> = 3)
Hewett <i>et al.</i> 2018 <sup>14</sup>	Symptomatic despite standard-of-care therapy. Eligible patients had a QMG total score of $\geq 8$ , of which $\geq 4$ points were derived from signs other than ocular	1	Phase II study ( <i>n</i> = 40)
Howard <i>et al.</i> 2013 <sup>15</sup>	Persistent moderate to severe muscle weakness despite treatment with $\geq 2$ immunosuppressive agents, including prednisone for $\geq 1$ year. Eligible patients had a QMG total score of $\geq 12$ and grade $\geq 2$ on $\geq 4$ QMG test items	1	Phase II study ( <i>n</i> = 14)
Howard <i>et al.</i> 2017 <sup>16</sup>	Eligible patients had an MG-ADL score of $\geq 6$ and MGFA class II–IV disease, and had received treatment with $\geq 2$ immunosuppressive therapies, or $\geq 1$ immunosuppressive therapy with IVIg or PE given $\geq 4$ times per year, for 12 months without symptom control	1,2	Phase III study ( <i>n</i> = 125)
Jing <i>et al.</i> 2017 <sup>17</sup>	Failure to respond to multiple immunosuppressive therapies, or unacceptable adverse reactions to conventional treatments, or requirement for repeated treatment with IVIg or PE, or frequent myasthenic crises	1,2,3,5	Small study ( <i>n</i> = 8)
Kanth <i>et al.</i> 2016 <sup>18</sup>	Multiple hospitalizations for MG exacerbations; multiple immunosuppressants; MMF stopped because of refractory symptoms, azathioprine stopped because of elevated liver function tests	1,3,5	Case of PML
Kovács <i>et al.</i> 2017 <sup>19</sup>	Case 1: inadequate response to multiple immunosuppressants including ciclosporin; need for PE or IVIg 2–3 times annually because of marked progression; inability to taper corticosteroids  Case 2: diagnosed with possible myositis; intolerance to azathioprine, inadequate response to hydroxychloroquine, methylprednisolone, and ciclosporin; PE for deteriorating symptoms	1,2  1,2,3	Case series ( <i>n</i> = 2)

Reference	Definition of refractory MG	Classification of definition <sup>a</sup>	Comment
Landon-Cardinal <i>et al.</i> 2018 <sup>20</sup>	Intolerance or inadequate response for >12 months to prednisone and $\geq 2$ other immunosuppressive and/or immunomodulatory agents during the year before inclusion  Inadequate response defined as the absence of improvement or worsening of MG signs and symptoms according to the MGFA postintervention status classification	1,3	Phase II study ( $n = 12$ )
Lebrun <i>et al.</i> 2009 <sup>21</sup>	Poor response to at least two successive immunosuppressive therapy schedules (azathioprine 150 mg/day, IV cyclophosphamide 500 mg/month, ciclosporin 100–200 mg/day, or MMF 2 g/day) after thymectomy associated with corticosteroids	1	Case series ( $n = 6$ )
Leuzzi <i>et al.</i> 2014 <sup>22</sup>	—		No definitions given; study ( $n = 177$ ) included patients with bulbar symptoms and patients undergoing plasmapheresis or IVIg treatment, suggesting patients with poorly controlled or refractory MG
Meriggioli and Rowin 2000 <sup>23</sup>	Persistent symptoms requiring hospitalization despite prednisolone, azathioprine; subsequent toxicity with azathioprine	1,3	Case history
Pompeo <i>et al.</i> 2000 <sup>24</sup>	Inclusion criteria for complete thymectomy: lack of significant symptomatic improvement for $\geq 3$ years after thymectomy; deterioration of symptoms after initial improvement lasting >24 months not adequately controlled by maximal medical therapy or requiring repeated PE cycles; evidence of residual thymic tissue or thymomatous transformation on computed tomography, magnetic resonance imaging, or both	1	Small study ( $n = 8$ )
Ponseti <i>et al.</i> 2005 <sup>25</sup>	All patients had MG symptoms despite prednisolone and ciclosporin treatment after thymectomy. Dose of prednisone or ciclosporin could not be reduced. All patients experienced side effects of long-term steroid and ciclosporin	1,2,3	Small study ( $n = 13$ )

Reference	Definition of refractory MG	Classification of definition <sup>a</sup>	Comment
	treatment including obesity, hypertrichosis, gingival enlargement, hypertension, hypercholesterolemia, and renal insufficiency		
Ponseti <i>et al.</i> 2005 <sup>26</sup>	As above	1,2,3	Prospective open-label study ( <i>n</i> = 79)
Rahul <i>et al.</i> 2017 <sup>27</sup>	Acute aggravation of MG refractory to usual treatment with multiple immunosuppressants, including IVIg, mycophenolate, prednisolone, and five cycles of plasmapheresis	1	Case history
Robeson <i>et al.</i> 2017 <sup>28</sup>	Immunotherapy dosage could not be lowered without clinical relapse, inadequate clinical control of the disease during the immunotherapy regimen, or severe adverse events due to current immunosuppressive therapy	1,2,3	Case series ( <i>n</i> = 16)
Schneider <i>et al.</i> 2001 <sup>29</sup>	Case 1: only moderate improvement in symptoms under treatment with pyridostigmine, glucocorticoids, azathioprine, and intermittent PE; azathioprine-associated liver toxicity	1,3	Case series ( <i>n</i> = 3)
	Case 2: worsening of bulbopharyngeal symptoms and weakness of respiratory muscles under treatment with azathioprine; liver toxicity resulting in stopping azathioprine; PE performed	1,3	
	Case 3: deterioration in muscle weakness under azathioprine and glucocorticoids (post-thymectomy)	1	
Sorgun <i>et al.</i> 2014 <sup>30</sup>	Inadequate response to standard therapies, and patients who could not or did not want to receive corticosteroid or immunosuppressive treatment owing to side effects	1,3	Small study ( <i>n</i> = 13)
Stieglbauer <i>et al.</i> 2017 <sup>31</sup>	Failure to respond adequately to conventional therapies and/or severe or intolerable side effects	1,3	Retrospective analysis ( <i>n</i> = 4), 10-year follow-up
Sudulagunta <i>et al.</i>	Immunotherapy for MG could not be reduced without clinical relapse; or MG not clinically controlled on immunotherapy regimen; or developed severe	1,2,3	Retrospective analysis ( <i>n</i> = 82)

Reference	Definition of refractory MG	Classification of definition <sup>a</sup>	Comment
2016 <sup>32</sup>	adverse events from immunosuppressive therapy for ≥12 months. Duration of treatment ≥1 year		
Yamada <i>et al.</i> 2015 <sup>33</sup>	Case 2: need for ongoing PE, serious adverse events related to PE Case 3: need for ongoing PE, serious adverse events related to azathioprine	2,3	Case series, MuSK-positive MG
Zieliński <i>et al.</i> 2004 <sup>34</sup>	Refractory myasthenic symptoms after a previous transsternal thymectomy, Osserman scale II–V; 67% receiving steroids or other immunosuppressive drugs	1	Small study ( <i>n</i> = 21)

<sup>a</sup>Classified according to definitions given in Table 1 in review article.

IV, intravenous; IVIg, intravenous immunoglobulin; MG, myasthenia gravis; MG-ADL, myasthenia gravis activities of daily living; MGFA, Myasthenia Gravis Foundation of America; MMF, mycophenolate mofetil; MuSK, muscle-specific kinase; PE, plasma exchange; PML, progressive multifocal leukoencephalopathy; QMG, quantitative myasthenia gravis.

**Supplementary Table 2.** Acute and long-term side effects of medications used to treat MG.

Drug <sup>a</sup> and dose <sup>b</sup>	AEs		Contraindications	Comments <sup>c</sup>	Illustrative examples in patients with MG
	Short term	Long term			
Acetylcholinesterase inhibitors					
<p>Pyridostigmine bromide</p> <p>Single dose orally: 30–60 mg; max. 360 mg/day</p> <p>Melzer <i>et al.</i> 2016;<sup>35</sup> Maggi and Mantegazza 2011;<sup>37</sup> Mylan Products Ltd 2018<sup>38</sup></p>	<p>Muscarinic effects (e.g. nausea, vomiting, diarrhea, abdominal cramps, increased peristaltic and bronchial secretions, increased salivation, miosis, heavy perspiration); nicotinic effects (e.g. muscle cramps, fasciculations, muscle weakness)</p>		<p>Mechanical gastrointestinal or urinary obstruction</p> <p>Extreme caution required when administering to patients with obstructive respiratory diseases</p> <p>Pregnancy; lactation</p>	<p>Poorly tolerated or may cause clinical worsening in patients with MuSK antibody-positive MG</p> <p>AEs occur in at least one-third of patients</p> <p>US Pregnancy Category C</p>	
<p>Ambenonium chloride</p> <p>Single dose orally: 5–10 mg; max. 40 mg/day</p> <p>Melzer <i>et al.</i> 2016;<sup>35</sup> Drugs.com 1994<sup>39</sup></p>	<p>Fewer gastrointestinal side effects than pyridostigmine</p>		<p>Routine administration with atropine</p> <p>Patients receiving mecamlamine or any other ganglionic-blocking agents</p>	<p>Not available in all countries</p> <p>Alternative agent for patients with an intolerance to pyridostigmine bromide</p> <p>US Pregnancy Category C</p>	
Systemic steroids					
<p>Glucocorticoids</p>	<p>Neuropsychiatric effects, gastrointestinal irritation,</p>	<p>Weight gain, diabetes mellitus, hypertension,</p>	<p>Systemic infections; ocular herpes simplex;</p>	<p>US Pregnancy Category C</p>	<p>Chronic steroid use provoked osteoporotic vertebral compression</p>

Drug <sup>a</sup> and dose <sup>b</sup>	AEs		Contraindications	Comments <sup>c</sup>	Illustrative examples in patients with MG
	Short term	Long term			
<p>Oral therapy: 0.5–1.5 mg/kg</p> <p>IV pulse therapy: 500–1000 mg/day for 1–3 days</p> <p>Melzer <i>et al.</i> 2016;<sup>35</sup> Moghadam-Kia and Werth 2010;<sup>40</sup> Accord-UK Ltd 2018;<sup>41</sup> Seton Pharmaceuticals 2013<sup>42</sup></p>	<p>skin disorders, susceptibility to infection, initial worsening of MG symptoms</p>	<p>myopathy, osteoporosis, cataracts, cushingoid appearance, steroid myopathy</p>	<p>patients with rare hereditary problems of galactose intolerance; the Lapp lactase deficiency or glucose-galactose malabsorption</p>		<p>fracture, cataract, and chronic central serous chorioretinopathy in a patient with refractory MG<sup>19</sup></p>
<b>Steroid-sparing immunosuppressants</b>					
<p>Methotrexate (off label)</p> <p>7.5–15 mg once per week; max. 25 mg once per week; in combination with folic acid (5 mg) 24 hours after application</p> <p>Melzer <i>et al.</i> 2016;<sup>35</sup> Hospira UK Ltd 2017;<sup>43</sup> Medac Pharma Inc. 2014<sup>44</sup></p>	<p>Gastrointestinal symptoms, interstitial pneumonitis, malaise, fatigue, chills, fever, dizziness, eye irritation, exanthema, leukopenia</p>	<p>Ulcerative stomatitis, myelosuppression, vasculitis, loss of libido/impotence, hepatotoxicity, kidney failure, pulmonary damage, fibrosis, psychiatric disorder, hair loss, osteoporosis, decreased resistance to infection</p>	<p>Active infections, immunodeficiency syndrome(s), renal insufficiency, liver insufficiency, alcohol abuse, pre-existing blood dyscrasias, pregnancy, breast feeding</p>	<p>US Pregnancy Category X</p>	<p>In clinical trials of methotrexate in patients with MG, AEs included nonspecific pain, gastrointestinal complaints, hypertension, and infections<sup>45,46</sup></p>
<p>MMF (off label)</p> <p>0.5–3 g/day in two single doses (mostly 2 × 1 g/day)</p> <p>Melzer <i>et al.</i> 2016;<sup>35</sup> Teva Pharma BV 2018;<sup>47</sup></p>	<p>Gastrointestinal symptoms, susceptibility to infection</p>	<p>Bone marrow suppression, risk for lymphoma, edema</p>	<p>Pregnancy, breast feeding</p>	<p>Multiple drug–drug interactions</p> <p>US Pregnancy Category D</p>	<p>In a phase III clinical trial in patients with MG, MMF was associated with headache, worsening of MG, and nausea; serious AEs occurred in 22% of patients,</p>



Drug <sup>a</sup> and dose <sup>b</sup>	AEs		Contraindications	Comments <sup>c</sup>	Illustrative examples in patients with MG
	Short term	Long term			
Genentech, Inc. 2015 <sup>48</sup>					including serious infections <sup>49</sup>  Other severe AEs reported in patients with MG receiving MMF include toxoplasmic encephalitis, chronic heart failure, primary CNS lymphoma, West Nile virus infection, severe depression, and severe skin reactions <sup>50–54</sup>
Tacrolimus (off label) 0.1–0.2 mg/day/kg in two single doses  Melzer <i>et al.</i> 2016; <sup>35</sup> Katari <i>et al.</i> 1997; <sup>55,56</sup> Sandoz Ltd 2017; <sup>57</sup> Astellas Pharma US, Inc. 2015 <sup>58</sup>	Opportunistic infections, nephrotoxicity, CNS toxicity (tremor, headache, posterior reversible encephalopathy syndrome), gastrointestinal conditions, hyperglycemic conditions, photophobia, tinnitus	PML, benign and malignant neoplasms, hepatotoxicity, hypertension, hyperkalemia, neurotoxicity, bone marrow suppression, diabetes mellitus, insomnia, skin rashes and erythema, gingival hyperplasia		Multiple drug–drug interactions  US Pregnancy Category C	In clinical trials in patients with MG, the most commonly occurring AEs (each occurring in approximately one-third of patients) were an increase in glycated hemoglobin level and an increase in neutrophil count <sup>59</sup>  Other reported AEs included nasopharyngitis (25% of patients), hypomagnesemia (24%), decreased

Drug <sup>a</sup> and dose <sup>b</sup>	AEs		Contraindications	Comments <sup>c</sup>	Illustrative examples in patients with MG
	Short term	Long term			
					lymphocyte count (5–37%), renal insufficiency (4%), and tremor (5%) <sup>59</sup>
<p>Azathioprine (off label in USA)</p> <p>Induction dose: 2–3 mg/day/kg</p> <p>Maintenance dose: 1.5–2 mg/day/kg</p> <p>Melzer <i>et al.</i> 2016;<sup>35</sup> Accord-UK Ltd 2017;<sup>60</sup> Prometheus Laboratories Inc. 2014<sup>61</sup></p>	<p>Viral, fungal, and bacterial infections, gastrointestinal conditions, myelosuppression, phototoxic reactions, hypersensitivity reactions</p>	<p>Pancreatitis, hepatotoxicity, cutaneous hyperkeratosis and skin malignancies</p>	<p>Hypersensitivity to azathioprine or 6-mercaptopurine; severe infections; seriously impaired hepatic or bone marrow function; pancreatitis; any live vaccine, especially BCG, smallpox, and yellow fever; pregnancy unless the benefits outweigh the risks; breast feeding</p>	<p>Multiple drug–drug interactions</p> <p>US Pregnancy Category D</p>	<p>AEs reported in case histories of patients with MG include intolerable nausea and abdominal pain, cytomegalovirus and parvovirus infections, and liver toxicity<sup>3,19,23,29,33</sup></p>
<p>Ciclosporin A (off label)</p> <p>2 (–5) mg/day/kg in two single doses</p> <p>Melzer <i>et al.</i> 2016;<sup>35</sup> Generics UK T/A Mylan 2015;<sup>62</sup> Novartis 2015<sup>63</sup></p>	<p>Opportunistic infection, nephrotoxicity, CNS toxicity (tremor, headache, posterior reversible encephalopathy syndrome), gastrointestinal conditions, hyperglycemic conditions, hyperlipidemia</p>	<p>PML, benign and malignant neoplasms, hepatotoxicity, hypertension, hyperkalemia, neurotoxicity, leukopenia, diabetes mellitus, skin rashes and erythema, gingival hyperplasia, hypertrichosis, hirsutism</p>	<p>Combination with products containing <i>Hypericum perforatum</i>; combination with medicines that are substrates for the multidrug efflux transporter P-glycoprotein or the organic anion transporter proteins and for which elevated plasma concentrations</p>	<p>Nephrotoxicity in approximately one-third of patients</p> <p>Multiple drug–drug interactions</p> <p>US Pregnancy Category C</p>	<p>In clinical trials of patients with MG who were treated with ciclosporin, the following AEs were reported to result in withdrawal: nephrotoxicity, headache, infection, and gastrointestinal events<sup>64,65</sup></p>

Drug <sup>a</sup> and dose <sup>b</sup>	AEs		Contraindications	Comments <sup>c</sup>	Illustrative examples in patients with MG
	Short term	Long term			
			are associated with serious and/or life-threatening events; abnormal renal function; uncontrolled hypertension; malignancies; pregnancy; breast feeding		
Escalation therapy					
Rituximab (off label) 1000 mg IV on days 1 and 15 every 6–9 months  Melzer <i>et al.</i> 2016; <sup>35</sup> Roche Products Ltd 2018; <sup>66</sup> Genentech, Inc. 2018 <sup>67</sup>	Infusion reaction, infections, Lyell's syndrome, Stevens–Johnson syndrome, cardiovascular events	PML, hepatitis B reactivation, severe mucocutaneous reactions	Active severe infections, severely immunocompromised state, severe heart failure or severe, uncontrolled cardiac disease, pregnancy (unless the possible benefit outweighs the potential risk), breast feeding	US Pregnancy Category C	In a large case series ( $n = 28$ ) of patients with refractory MG who were treated with rituximab, 39% were reported as having 'benign' side effects such as flu-like syndrome, while 14% had severe side effects <sup>1</sup>  One case of PML was identified in a systematic review of 47 uncontrolled observational studies and case histories comprising a total of 169 patients treated

Drug <sup>a</sup> and dose <sup>b</sup>	AEs		Contraindications	Comments <sup>c</sup>	Illustrative examples in patients with MG
	Short term	Long term			
					with rituximab <sup>68</sup>  One case of PML was also diagnosed in a patient with refractory MG who had received long-term rituximab <sup>1</sup>
<p>Eculizumab</p> <p>Initial phase: 900 mg <i>via</i> a 25- to 45-minute IV infusion every week for the first 4 weeks</p> <p>Maintenance phase: 1200 mg <i>via</i> a 25- to 45-minute IV infusion on week 5, followed by 1200 mg <i>via</i> a 25- to 45-minute IV infusion every 14 ± 2 days</p> <p>Alexion Pharma UK Ltd 2017;<sup>36</sup> Dhillon 2018<sup>69</sup></p>	<p>Meningococcal infections, other infections, headache, diarrhea</p>	<p>Arthralgia</p>	<p>Unresolved <i>Neisseria meningitidis</i> infection; patients not currently vaccinated against <i>N. meningitidis</i> unless they receive prophylactic treatment with appropriate antibiotics until 2 weeks after vaccination</p>	<p>Meningococcal infection was uncommon (i.e. incidence of ≥1/1000 to &lt;1/100) in 1407 patients included in 29 eculizumab clinical trials, including patients with paroxysmal nocturnal hemoglobinuria, atypical hemolytic uremic syndrome, and refractory generalized MG, as well as from postmarketing experience<sup>70</sup></p> <p>No meningococcal infections were reported in completed refractory MG clinical studies in which patients received prophylactic antibiotic treatment or</p>	<p>Phase III trial: the most common AEs associated with eculizumab were reported with similar frequency in patients receiving placebo: headache (16% with eculizumab <i>versus</i> 19% with placebo), upper respiratory tract infection (16% <i>versus</i> 19%), nasopharyngitis (15% <i>versus</i> 16%), nausea (13% <i>versus</i> 14%), and diarrhea (13% <i>versus</i> 13%)<sup>16</sup></p> <p>Serious AEs (mainly infections) occurred in 15% of patients receiving eculizumab (<i>versus</i> 29% receiving placebo)<sup>16</sup></p> <p>Similar AEs were</p>

Drug <sup>a</sup> and dose <sup>b</sup>	AEs		Contraindications	Comments <sup>c</sup>	Illustrative examples in patients with MG
	Short term	Long term			
				<p>vaccination</p> <p>According to the Centers for Disease Control and Prevention, 16 cases of meningococcal disease (including one fatality) were identified in patients in the USA who received eculizumab (mainly for paroxysmal nocturnal hemoglobinuria) between 2008 and 2016<sup>71</sup></p>	<p>reported in the extension study: headache (27%), nasopharyngitis (24%), and diarrhea (14%)<sup>72</sup></p>
<p>Cyclophosphamide (off label)</p> <p>Pulse therapy: 500–750 mg/m<sup>2</sup> IV every 4–8 weeks under urothelial protection with mesna</p> <p>Melzer <i>et al.</i> 2016;<sup>35</sup> Sandoz Ltd 2017;<sup>73</sup> Baxter International Inc. 2013<sup>74</sup></p>	<p>Gastrointestinal symptoms, infection, fever, chills, asthenia, malaise, alopecia, cystitis</p>	<p>Liver dysfunction, bone marrow suppression, malignancies</p>	<p>Acute infections, bone marrow aplasia or bone marrow depression, urinary tract infection, urinary outflow obstruction, pregnancy, breast feeding</p>	<p>US Pregnancy Category D</p>	<p>High-dose cyclophosphamide treatment resulted in neutropenic fever in 7/12 patients (58%) with refractory MG, resulting in readmission to hospital for antibiotic treatment<sup>75</sup></p> <p>In four of these patients, neutropenic fever was attributable to diverticulitis, axilla abscess, line infection, and mycoplasma</p>

Drug <sup>a</sup> and dose <sup>b</sup>	AEs		Contraindications	Comments <sup>c</sup>	Illustrative examples in patients with MG
	Short term	Long term			
					pneumonitis; the cause was unknown in the other three patients <sup>75</sup>
Intervention therapies					
IVIg (off label) 0.4 g/kg/day on 5 consecutive days, or 1 g/kg/day on 2 consecutive days  Melzer <i>et al.</i> 2016; <sup>35</sup> Sanders <i>et al.</i> 2016; <sup>76</sup> Gajdos <i>et al.</i> 2012; <sup>77</sup> Barth <i>et al.</i> 2011 <sup>78</sup>	Headache, fever or chills, nausea, hypertension, allergic/anaphylactic reactions, dermatitis, pulmonary edema, venous thrombosis, aseptic meningitis, hemolysis, serum creatinine concentration elevations	Infection (HIV or viral hepatitis)	Renal failure, hypercoagulable states, hypersensitivity to immunoglobulin		AEs associated with IVIg in clinical trials in patients with MG include moderate fever, nausea, and headache <sup>77</sup>  Delayed AEs may include thrombotic events (including stroke), neurological disorders, renal impairment, hematologic disorders, electrolyte disturbance, aseptic meningitis, and transfusion-related infection <sup>79</sup>
Plasmapheresis  Gajdos <i>et al.</i> 2012; <sup>77</sup> Barth <i>et al.</i> 2011; <sup>78</sup> Heatwole <i>et al.</i> 2011; <sup>80</sup> Köhler <i>et al.</i> 2011 <sup>81</sup>	Arterial bleeding, bleeding disorders, infections, septicemia, venous thrombosis, nausea, hypotension, citrate	Sepsis	Sepsis		Individual cases of catheter-related infection and sepsis, alterations in hemostasis and

Drug <sup>a</sup> and dose <sup>b</sup>	AEs		Contraindications	Comments <sup>c</sup>	Illustrative examples in patients with MG
	Short term	Long term			
	reaction, vasospasm, vasovagal reaction				hydrothorax in patients with refractory MG treated with PE <sup>19,33</sup>  AEs in clinical studies in patients with MG treated with PE include hypotension, hemolysis, hematoma, septicemia, fever, and thrombosis <sup>81,82</sup>
Immunoadsorption Köhler <i>et al.</i> 2011 <sup>81</sup>	Tachycardia, bradycardia, hypotension, dyspnea, hemorrhage		Sepsis (depending on clinical condition)		

<sup>a</sup>Designated 'off label' if not indicated for use in MG in Europe and/or the USA.

<sup>b</sup>Melzer *et al* 2016;<sup>35</sup> except eculizumab: Alexion Pharma UK Ltd 2017.<sup>36</sup>

<sup>c</sup>Pregnancy categories no longer assigned in the USA after 30 June 2015.

AE, adverse event; BCG, bacillus Calmette-Guérin; CNS, central nervous system; HIV, human immunodeficiency virus; IV, intravenous; IVIg, intravenous immunoglobulin; MG, myasthenia gravis; MMF, mycophenolate mofetil; MuSK, muscle-specific kinase; PE, plasma exchange; PML, progressive multifocal leukoencephalopathy; USA, United States of America.

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