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Symptomatic treatment of myasthenia gravis and its role in the era of emerging immunomodulatory treatments

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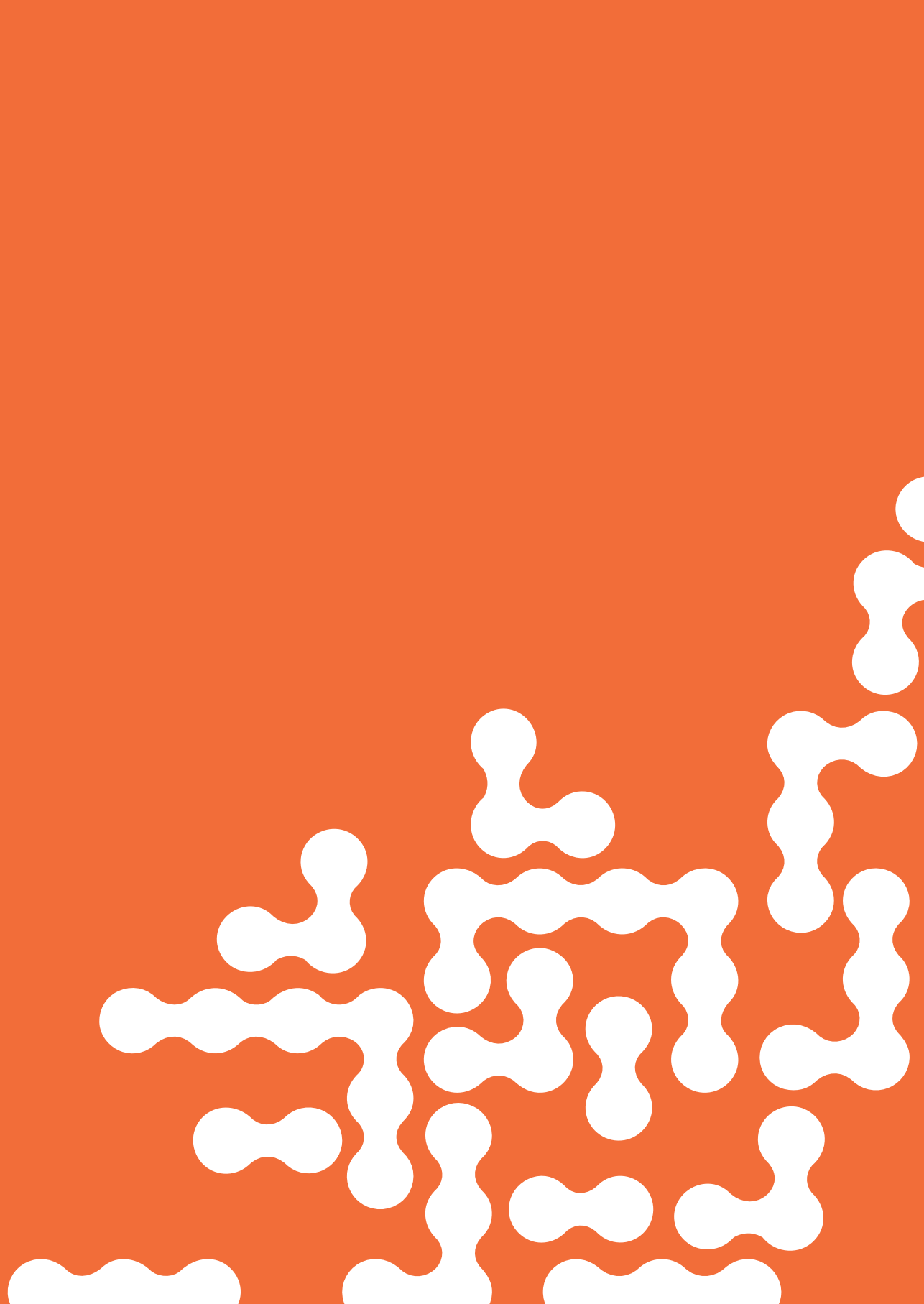
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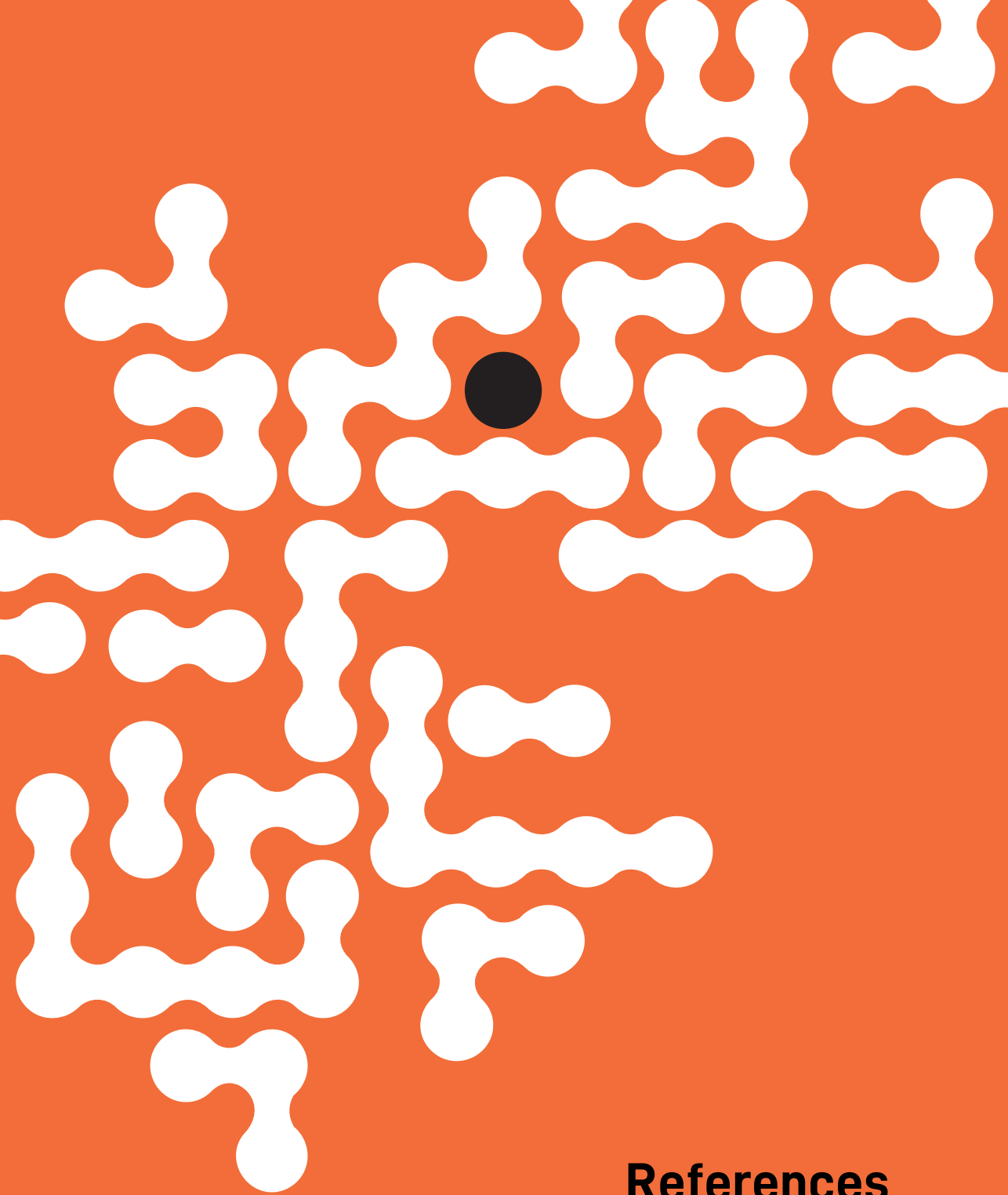
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References

REFERENCES

1. Gilhus NE, Tzartos S, Evoli A, Palace J, Burns TM, Verschuuren J. Myasthenia gravis. *Nat Rev Dis Primers* 2019; **5**(1): 30.
2. Punga AR, Maddison P, Heckmann JM, Guptill JT, Evoli A. Epidemiology, diagnostics, and biomarkers of autoimmune neuromuscular junction disorders. *Lancet Neurol* 2022; **21**(2): 176–88.
3. Gilhus NE, Verschuuren JJ. Myasthenia gravis: subgroup classification and therapeutic strategies. *Lancet Neurol* 2015; **14**(10): 1023–36.
4. Sciancalepore F, Lombardi N, Valdiserra G, et al. Prevalence, Incidence, and Mortality of Myasthenia Gravis and Myasthenic Syndromes: A Systematic Review. *Neuroepidemiology* 2024; 1–14.
5. Gilhus NE. Myasthenia Gravis. *N Engl J Med* 2016; **375**(26): 2570–81.
6. Huijbers MG, Marx A, Plomp JJ, Le Panse R, Phillips WD. Advances in the understanding of disease mechanisms of autoimmune neuromuscular junction disorders. *Lancet Neurol* 2022; **21**(2): 163–75.
7. Rodríguez Cruz PM, Cossins J, Beeson D, Vincent A. The Neuromuscular Junction in Health and Disease: Molecular Mechanisms Governing Synaptic Formation and Homeostasis. *Frontiers in Molecular Neuroscience* 2020; **Volume 13** - 2020.
8. Plomp JJ, Morsch M, Phillips WD, Verschuuren JJ. Electrophysiological analysis of neuromuscular synaptic function in myasthenia gravis patients and animal models. *Exp Neurol* 2015; **270**: 41–54.
9. Huang K, Luo YB, Yang H. Autoimmune Channelopathies at Neuromuscular Junction. *Front Neurol* 2019; **10**: 516.
10. Phillips W, Vincent A. Pathogenesis of myasthenia gravis: update on disease types, models, and mechanisms [version 1; peer review: 2 approved]. *F1000Research* 2016; **5**(1513).
11. Koneczny I, Herbst R. Myasthenia Gravis: Pathogenic Effects of Autoantibodies on Neuromuscular Architecture. *Cells* 2019; **8**(7).
12. Fichtner ML, Jiang R, Bourke A, Nowak RJ, O'Connor KC. Autoimmune Pathology in Myasthenia Gravis Disease Subtypes Is Governed by Divergent Mechanisms of Immunopathology. *Frontiers in Immunology* 2020; **11**.
13. Li H, Pham MC, Teng J, O'Connor KC, Noviello CM, Hibbs RE. Autoimmune mechanisms elucidated through muscle acetylcholine receptor structures. *Cell* 2025; **188**(9): 2390–406.e20.
14. Pham MC, Masi G, Patzina R, et al. Individual myasthenia gravis autoantibody clones can efficiently mediate multiple mechanisms of pathology. *Acta Neuropathologica* 2023; **146**(2): 319–36.
15. Huijbers MG, Zhang W, Klooster R, et al. MuSK IgG4 autoantibodies cause myasthenia gravis by inhibiting binding between MuSK and Lrp4. *Proc Natl Acad Sci U S A* 2013; **110**(51): 20783–8.
16. Burden SJ, Huijbers MG, Remedio L. Fundamental Molecules and Mechanisms for Forming and Maintaining Neuromuscular Synapses. *Int J Mol Sci* 2018; **19**(2).
17. Pegat A, Gavaille A, Bonjour M, et al. Is the decrement pattern in myasthenia gravis due to muscle-specific kinase antibodies different to that due to acetylcholine receptor antibodies? *Neurophysiologie Clinique* 2025; **55**(6): 103092.
18. Kawakami Y, Ito M, Hirayama M, et al. Anti-MuSK autoantibodies block binding of collagen Q to MuSK. *Neurology* 2011; **77**(20): 1819–26.
19. Kaminski HJ, Sikorski P, Coronel SJ, Kusner LL. Myasthenia gravis: the future is here. *J Clin Invest* 2024; **134**(12).
20. Suzuki S. Pathogenesis and detection methods of anti-acetylcholine receptor antibodies in myasthenia gravis. *Immunological Medicine* 2025; **48**(2): 117–23.
21. Cavalcante P, Le Panse R, Berrih-Aknin S, et al. The thymus in myasthenia gravis: Site of “innate autoimmunity”? *Muscle Nerve* 2011; **44**(4): 467–84.
22. Lauriola L, Ranalletti F, Maggiano N, et al. Thymus changes in anti-MuSK-positive and -negative myasthenia gravis. *Neurology* 2005; **64**(3): 536–8.
23. 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**(4): 404–10.
24. Kushlaf H, Li Y. The evidence is stacked against thymectomy in MuSK myasthenia gravis. *Muscle Nerve* 2019; **59**(4): 393–4.
25. Sanders DB, Wolfe GI, Benatar M, et al. International consensus guidance for management of myasthenia gravis: Executive summary. *Neurology* 2016; **87**(4): 419–25.
26. Skeie GO, Apostolski S, Evoli A, et al. Guidelines for treatment of autoimmune neuromuscular transmission disorders. *Eur J Neurol* 2010; **17**(7): 893–902.

27. Wiendl H, Abicht A, Chan A, et al. Guideline for the management of myasthenic syndromes. *Ther Adv Neurol Disord* 2023; **16**: 17562864231213240.
28. Spierziekten Centrum Nederland. Consensus richtlijn Autoimmuun Myasthenia Gravis. 2025; **Versie 2.0**.
29. Katz NK, Barohn RJ. The history of acetylcholinesterase inhibitors in the treatment of myasthenia gravis. *Neuropharmacology* 2021; **182**: 108303.
30. Mehndiratta MM, Pandey S, Kuntzer T. Acetylcholinesterase inhibitor treatment for myasthenia gravis. *Cochrane Database Syst Rev* 2014; (10): CD006986.
31. Lipka AF, Vrinten C, van Zwet EW, et al. Ephedrine treatment for autoimmune myasthenia gravis. *Neuromuscul Disord* 2017; **27**(3): 259–65.
32. Bonanno S, Pasanisi MB, Frangiamore R, et al. Amifampridine phosphate in the treatment of muscle-specific kinase myasthenia gravis: a phase IIb, randomized, double-blind, placebo-controlled, double crossover study. *SAGE Open Med* 2018; **6**: 2050312118819013.
33. Evoli A, Alboini PE, Damato V, Iorio R. 3,4-Diaminopyridine may improve myasthenia gravis with MuSK antibodies. *Neurology* 2016; **86**(11): 1070–1.
34. Lee MK, Sunwoo IN, Kim SM. 3,4-Diaminopyridine for the treatment of myasthenia gravis with electrophysiological patterns of Lambert-Eaton myasthenic syndrome. *J Clin Neurosci* 2018; **50**: 194–8.
35. Keesey JC. A history of treatments for myasthenia gravis. *Semin Neurol* 2004; **24**(1): 5–16.
36. Overhaus M, Kaminski M, Hirner A, Schäfer N. [The history of thymus surgery]. *Chirurg* 2007; **78**(10): 950–3.
37. Wolfe GI, Kaminski HJ, Aban IB, et al. Randomized Trial of Thymectomy in Myasthenia Gravis. *New England Journal of Medicine* 2016; **375**(6): 511–22.
38. Wolfe GI, Kaminski HJ, Aban IB, et al. Long-term effect of thymectomy plus prednisone versus prednisone alone in patients with non-thymomatous myasthenia gravis: 2-year extension of the MGTX randomised trial. *Lancet Neurol* 2019; **18**(3): 259–68.
39. Verschuuren JJ, Palace J, Murai H, Tannemaat MR, Kaminski HJ, Bril V. Advances and ongoing research in the treatment of autoimmune neuromuscular junction disorders. *Lancet Neurol* 2022; **21**(2): 189–202.
40. Kaminski HJ, Denk J. Corticosteroid Treatment-Resistance in Myasthenia Gravis. *Frontiers in Neurology* 2022; **Volume 13 - 2022**.
41. Schneider-Gold C, Gajdos P, Toyka KV, Hohlfeld RR. Corticosteroids for myasthenia gravis. *Cochrane Database Syst Rev* 2005; **2005**(2): Cd002828.
42. Bacher C, Narayanswami P, Bromberg M, et al. International Consensus Guidance for the Management of Glucocorticoid Related Complications in Neuromuscular Disease. *Muscle Nerve* 2025; **71**(3): 309–16.
43. Gilhus NE, Andersen H, Andersen LK, et al. Generalized myasthenia gravis with acetylcholine receptor antibodies: A guidance for treatment. *Eur J Neurol* 2024; **31**(5): e16229.
44. Palace J, Newsom-Davis J, Lecky B. A randomized double-blind trial of prednisolone alone or with azathioprine in myasthenia gravis. Myasthenia Gravis Study Group. *Neurology* 1998; **50**(6): 1778–83.
45. Muscle Study G. A trial of mycophenolate mofetil with prednisone as initial immunotherapy in myasthenia gravis. *Neurology* 2008; **71**(6): 394–9.
46. Sanders DB, Hart IK, Mantegazza R, et al. An international, phase III, randomized trial of mycophenolate mofetil in myasthenia gravis. *Neurology* 2008; **71**(6): 400–6.
47. Sanders DB, Siddiqi ZA. Lessons from two trials of mycophenolate mofetil in myasthenia gravis. *Ann N Y Acad Sci* 2008; **1132**: 249–53.
48. Heckmann JM, Rawoot A, Bateman K, Renison R, Badri M. A single-blinded trial of methotrexate versus azathioprine as steroid-sparing agents in generalized myasthenia gravis. *BMC Neurol* 2011; **11**: 97.
49. Pasnoor M, He J, Herbelin L, et al. A randomized controlled trial of methotrexate for patients with generalized myasthenia gravis. *Neurology* 2016; **87**(1): 57–64.
50. Dodd KC, Ahmed R, Ambrose P, et al. Mycophenolate and methotrexate are better tolerated than azathioprine in myasthenia gravis. *Neuromuscul Disord* 2024; **38**: 51–7.
51. Narayanaswami P, Sanders DB, Thomas L, et al. Comparative effectiveness of azathioprine and mycophenolate mofetil for myasthenia gravis (PROMISE-MG): a prospective cohort study. *Lancet Neurol* 2024; **23**(3): 267–76.
52. Vos M, Plasmeijer EI, van Bemmelen BC, et al. Azathioprine to mycophenolate mofetil transition and risk of squamous cell carcinoma after lung transplantation. *J Heart Lung Transplant* 2018; **37**(7): 853–9.
53. Ghimire A, Kunwar B, Aryal B, et al. Assessing the comparative efficacy of plasmapheresis and Intravenous

- immunoglobulin in myasthenia gravis treatment: A systematic review and meta-analysis. *J Clin Neurosci* 2024; **121**: 1–10.
54. Pavlekovic M, Engh MA, Lugosi K, et al. Plasma Exchange versus Intravenous Immunoglobulin in Worsening Myasthenia Gravis: A Systematic Review and Meta-Analysis with Special Attention to Faster Relapse Control. *Biomedicines* 2023; **11**(12).
 55. Bril V, Szczudlik A, Vaitkus A, et al. Randomized Double-Blind Placebo-Controlled Trial of the Corticosteroid-Sparing Effects of Immunoglobulin in Myasthenia Gravis. *Neurology* 2023; **100**(7): e671–e82.
 56. Bril V, Berkowicz T, Szczudlik A, et al. Efficacy and safety of maintenance intravenous immunoglobulin in generalized myasthenia gravis patients with acetylcholine receptor antibodies: A multicenter, double-blind, placebo-controlled trial. *Muscle Nerve* 2025; **71**(1): 43–54.
 57. 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**(12): 976–86.
 58. Muppidi S, Utsugisawa K, Benatar M, et al. Long-term safety and efficacy of eculizumab in generalized myasthenia gravis. *Muscle Nerve* 2019; **60**(1): 14–24.
 59. Vu T, Meisel A, Mantegazza R, et al. Terminal Complement Inhibitor Ravulizumab in Generalized Myasthenia Gravis. *NEJM Evidence* 2022; **1**(5): EVIDoa2100066.
 60. Howard JF, Jr., Bresch S, Genge A, et al. Safety and efficacy of zilucoplan in patients with generalised myasthenia gravis (RAISE): a randomised, double-blind, placebo-controlled, phase 3 study. *Lancet Neurol* 2023; **22**(5): 395–406.
 61. Wolfe GI, Ward ES, de Haard H, et al. IgG regulation through FcRn blocking: A novel mechanism for the treatment of myasthenia gravis. *J Neurol Sci* 2021; **430**: 118074.
 62. 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**(7): 526–36.
 63. Howard JF, Bril V, Vu T, et al. Long-term safety, tolerability, and efficacy of efgartigimod (ADAPT+): interim results from a phase 3 open-label extension study in participants with generalized myasthenia gravis. *Frontiers in Neurology* 2024; **14**.
 64. Bril V, Drużdż A, Grosskreutz J, et al. Safety and efficacy of rozanolixizumab in patients with generalised myasthenia gravis (MycarinG): a randomised, double-blind, placebo-controlled, adaptive phase 3 study. *Lancet Neurol* 2023; **22**(5): 383–94.
 65. Antozzi C, Vu T, Ramchandren S, et al. Safety and efficacy of nipocalimab in adults with generalised myasthenia gravis (Vivacity-MG3): a phase 3, randomised, double-blind, placebo-controlled study. *Lancet Neurol* 2025; **24**(2): 105–16.
 66. Dresser L, Wlodarski R, Rezania K, Soliven B. Myasthenia Gravis: Epidemiology, Pathophysiology and Clinical Manifestations. *J Clin Med* 2021; **10**(11).
 67. Borges LS, Richman DP. Muscle-Specific Kinase Myasthenia Gravis. *Front Immunol* 2020; **11**: 707.
 68. Walker MB. Treatment of myasthenia gravis with physostigmine. *The Lancet* 1934: 1200–1.
 69. Schwab RS, Timberlake WH. Pyridostigmin (mestinon) in the treatment of myasthenia gravis. *N Engl J Med* 1954; **251**(7): 271–2.
 70. Schwarz H. Mestinon (pyridostigmine bromide) in myasthenia gravis. *Can Med Assoc J* 1956; **75**(2): 98–100.
 71. Tether JE. Treatment of myasthenia gravis with mestinon bromide. *J Am Med Assoc* 1956; **160**(3): 156–8.
 72. Westerberg MR, Magee KR. Mestinon in the treatment of myasthenia gravis. *Neurology* 1954; **4**(10): 762–72.
 73. Osserman KE, Teng P, Kaplan LI. Studies in myasthenia gravis; preliminary report on therapy with mestinon bromide. *J Am Med Assoc* 1954; **155**(11): 961–5.
 74. Berrih-Aknin S, Frenkian-Cuvelier M, Eymard B. Diagnostic and clinical classification of autoimmune myasthenia gravis. *J Autoimmun* 2014; **48-49**: 143–8.
 75. Engel AG, Lambert EH, Santa T. Study of long-term anticholinesterase therapy. Effects on neuromuscular transmission and on motor end-plate fine structure. *Neurology* 1973; **23**(12): 1273–81.
 76. Gillies JD, Allen J. Effects of neostigmine and pyridostigmine at the neuromuscular junction. *Clin Exp Neurol* 1977; **14**: 271–9.
 77. Punga AR, Sawada M, Stalberg EV. Electrophysiological signs and the prevalence of adverse effects of acetylcholinesterase inhibitors in patients with myasthenia gravis. *Muscle Nerve* 2008; **37**(3): 300–7.

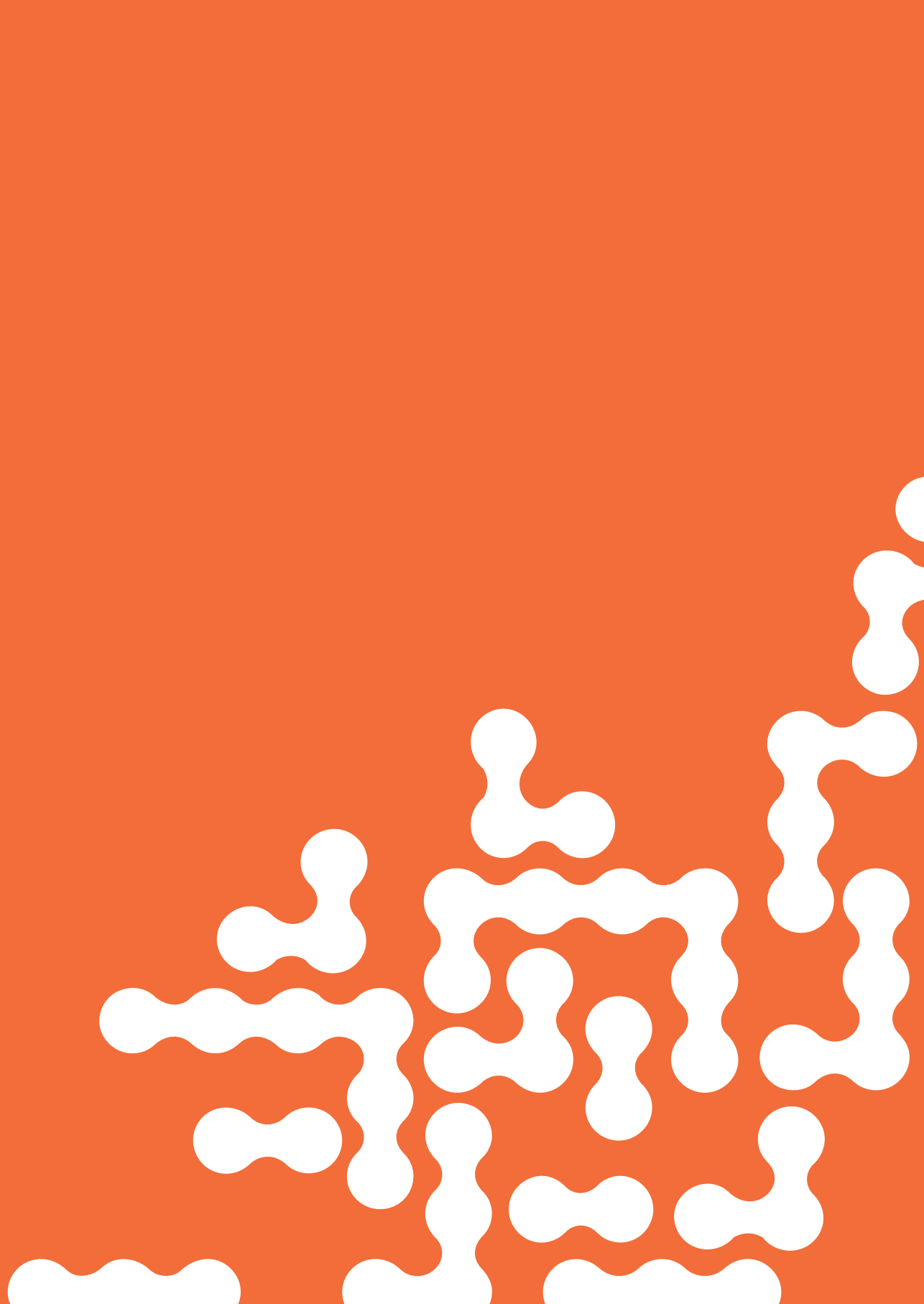
78. Beeson D. Congenital myasthenic syndromes: recent advances. *Curr Opin Neurol* 2016; **29**(5): 565–71.
79. Remijn-Nelissen L, Verschuuren J, Tannemaat MR. The effectiveness and side effects of pyridostigmine in the treatment of myasthenia gravis: a cross-sectional study. *Neuromuscul Disord* 2022; **32**(10): 790–9.
80. Bricher Choque PN, Vieira RP, Ulloa L, et al. The Cholinergic Drug Pyridostigmine Alleviates Inflammation During LPS-Induced Acute Respiratory Distress Syndrome. *Front Pharmacol* 2021; **12**: 624895.
81. Vaknine S, Soreq H. Central and peripheral anti-inflammatory effects of acetylcholinesterase inhibitors. *Neuropharmacology* 2020; **168**: 108020.
82. Lv J, Ji X, Li Z, Hao H. The role of the cholinergic anti-inflammatory pathway in autoimmune rheumatic diseases. *Scand J Immunol* 2021; **94**(4): e13092.
83. Kerty E, Elsaïs A, Argov Z, Evoli A, Gilhus NE. EFNS/ENS Guidelines for the treatment of ocular myasthenia. *Eur J Neurol* 2014; **21**(5): 687–93.
84. 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**(8): 1473–94.
85. Sussman J, Farrugia ME, Maddison P, Hill M, Leite MI, Hilton-Jones D. Myasthenia gravis: Association of British Neurologists' management guidelines. *Pract Neurol* 2015; **15**(3): 199–206.
86. Ruiter AM, Strijbos E, de Meel RHP, et al. Accuracy of patient-reported data for an online patient registry of autoimmune myasthenia gravis and Lambert-Eaton myasthenic syndrome. *Neuromuscul Disord* 2021; **31**(7): 622–32.
87. Machado-Alba JE, Calvo-Torres LF, Gaviria-Mendoza A, Augusto Mejí AVC. Prescription profile of pyridostigmine use in a population of patients with myasthenia gravis. *Muscle Nerve* 2017; **56**(6): 1041–6.
88. Sobieszczuk E, Napiórkowski Ł, Szczudlik P, Kostera-Pruszycki A. Myasthenia gravis-treatment and severity in nationwide cohort. *Acta Neurol Scand* 2022; **145**(4): 471–8.
89. Farrugia ME, Goodfellow JA. A Practical Approach to Managing Patients With Myasthenia Gravis-Opinions and a Review of the Literature. *Front Neurol* 2020; **11**: 604.
90. Evoli A, Bianchi MR, Riso R, et al. Response to therapy in myasthenia gravis with anti-MuSK antibodies. *Ann N Y Acad Sci* 2008; **1132**: 76–83.
91. Richman DP, Agius MA. Treatment of autoimmune myasthenia gravis. *Neurology* 2003; **61**(12): 1652–61.
92. Gehl A, Benatar M, Langberg J. Treatment of pyridostigmine-induced AV block with hyoscyamine in a patient with myasthenia gravis. *J Cardiovasc Electrophysiol* 2008; **19**(2): 214–6.
93. Schwab RS, Marshall CK, Timberlake W. WIN 8077 in treatment of myasthenia gravis; use of N,N'-bis (2-diethylaminoethyl) oxamide bis-2-chlorobenzyl chloride in fifty patients. *J Am Med Assoc* 1955; **158**(8): 625–8.
94. Westerberg MR. Clinical evaluation of ambenonium (mysuran) chloride. *AMA Arch Neurol Psychiatry* 1956; **75**(1): 91–4.
95. Tharasse-Bloch C, Chabenat C, Boucly P, et al. Pharmacokinetic studies of ambenonium chloride in patients with myasthenia gravis. *Eur J Drug Metab Pharmacokinet* 1991; **16**(4): 299–303.
96. EMA. Summary of Product Characteristics: Firdapse EMEA/H/C/001032 - S/0066. 26-11-2020 2010 (accessed 16-06-2021).
97. Sanders DB, Howard JF, Jr., Massey JM. 3,4-Diaminopyridine in Lambert-Eaton myasthenic syndrome and myasthenia gravis. *Ann N Y Acad Sci* 1993; **681**: 588–90.
98. Wirtz PW, Verschuuren JJ, van Dijk JG, et al. Efficacy of 3,4-diaminopyridine and pyridostigmine in the treatment of Lambert-Eaton myasthenic syndrome: a randomized, double-blind, placebo-controlled, crossover study. *Clin Pharmacol Ther* 2009; **86**(1): 44–8.
99. Lundh H, Nilsson O, Rosen I. Improvement in neuromuscular transmission in myasthenia gravis by 3,4-diaminopyridine. *Eur Arch Psychiatry Neurol Sci* 1985; **234**(6): 374–7.
100. Engel AG, Shen XM, Selcen D, Sine SM. Congenital myasthenic syndromes: pathogenesis, diagnosis, and treatment. *Lancet Neurol* 2015; **14**(5): 461.
101. McMacken G, Cox D, Roos A, Müller J, Whittaker R, Lochmüller H. The beta-adrenergic agonist salbutamol modulates neuromuscular junction formation in zebrafish models of human myasthenic syndromes. *Hum Mol Genet* 2018; **27**(9): 1556–64.
102. Clausen L, Cossins J, Beeson D. Beta-2 Adrenergic Receptor Agonists Enhance AChR Clustering in C2C12 Myotubes: Implications for Therapy of Myasthenic Disorders. *J Neuromuscul Dis* 2018; **5**(2): 231–40.
103. Farmakidis C, Pasnoor M, Barohn RJ, Dimachkie MM. Congenital Myasthenic Syndromes: a Clinical and Treatment Approach. *Curr Treat Options Neurol* 2018; **20**(9): 36.

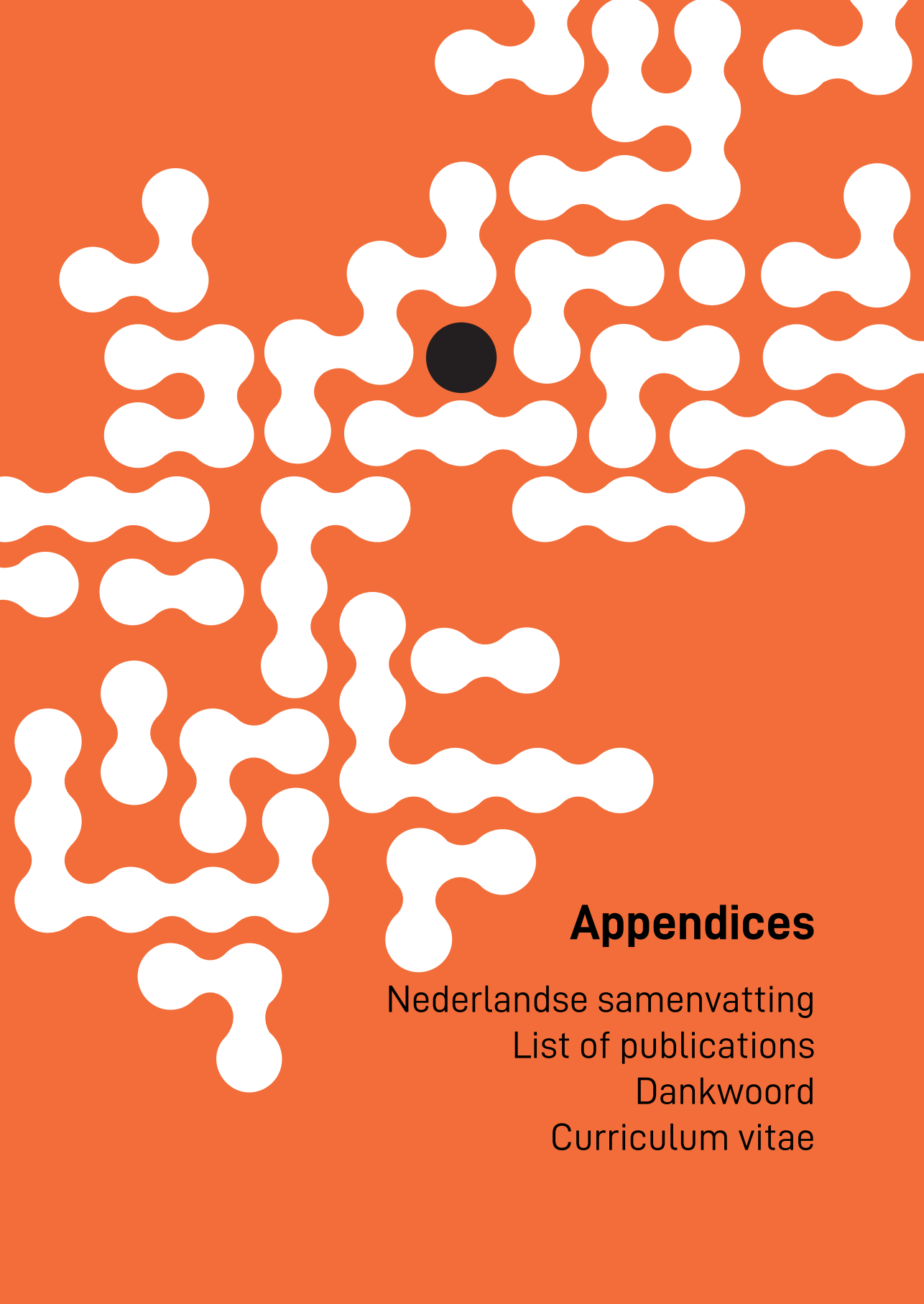
104. Bukharaeva E, Khuzakhmetova V, Dmitrieva S, Tsentsevitsky A. Adrenoceptors Modulate Cholinergic Synaptic Transmission at the Neuromuscular Junction. *International Journal of Molecular Sciences* 2021; **22**(9): 4611.
105. Rodrigues AZC, Wang ZM, Messi ML, Delbono O. Sympathomimetics regulate neuromuscular junction transmission through TRPV1, P/Q- and N-type Ca(2+) channels. *Mol Cell Neurosci* 2019; **95**: 59–70.
106. Elenkov IJ, Wilder RL, Chrousos GP, Vizi ES. The sympathetic nerve—an integrative interface between two supersystems: the brain and the immune system. *Pharmacol Rev* 2000; **52**(4): 595–638.
107. Kohm AP, Sanders VM. Norepinephrine and beta 2-adrenergic receptor stimulation regulate CD4+ T and B lymphocyte function in vitro and in vivo. *Pharmacol Rev* 2001; **53**(4): 487–525.
108. Vrinten C, van der Zwaag AM, Weinreich SS, Scholten RJ, Verschuuren JJ. Ephedrine for myasthenia gravis, neonatal myasthenia and the congenital myasthenic syndromes. *Cochrane Database Syst Rev* 2014; **2014**(12): CD010028.
109. Edgeworth H. A REPORT OF PROGRESS ON THE USE OF EPHEDRINE IN A CASE OF MYASTHENIA GRAVIS. *Journal of the American Medical Association* 1930; **94**(15): 1136–.
110. Vanhaesebrouck AE, Webster R, Maxwell S, et al. β 2-Adrenergic receptor agonists ameliorate the adverse effect of long-term pyridostigmine on neuromuscular junction structure. *Brain* 2019; **142**(12): 3713–27.
111. Chelmicka-Schorr E, Wollmann RL, Kwasniewski MN, Kim DH, Dupont BL. The beta 2-adrenergic agonist terbutaline suppresses acute passive transfer experimental autoimmune myasthenia gravis (EAMG). *Int J Immunopharmacol* 1993; **15**(1): 19–24.
112. Soliven B, Rezanian K, Gundogdu B, Harding-Clay B, Oger J, Arnason BG. Terbutaline in myasthenia gravis: a pilot study. *J Neurol Sci* 2009; **277**(1–2): 150–4.
113. Pedersen TH, Macdonald WA, Broch-Lips M, Halldorsdottir O, Baekgaard Nielsen O. Chloride channel inhibition improves neuromuscular function under conditions mimicking neuromuscular disorders. *Acta Physiol (Oxf)* 2021; **233**(2): e13690.
114. NMD Pharma. Reports Positive Top-Line Data from a Phase I/IIa Clinical Trial of NMD670 in Patients with Myasthenia Gravis. 2022, October 11. <https://www.nmdpharma.com/news/nmd670-top-line-data> (accessed 2023, February 20)
115. Russell AJ, Hartman JJ, Hinken AC, et al. Activation of fast skeletal muscle troponin as a potential therapeutic approach for treating neuromuscular diseases. *Nat Med* 2012; **18**(3): 452–5.
116. Sanders DB, Rosenfeld J, Dimachkie MM, Meng L, Malik FI, Tirasemtiv in Myasthenia Gravis Study G. 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**(2): 455–60.
117. Shefner JM, Cudkowicz ME, Hardiman O, et al. A phase III trial of tirasemtiv as a potential treatment for amyotrophic lateral sclerosis. *Amyotroph Lateral Scler Frontotemporal Degener* 2019; **0**(0): 1–11.
118. Andrews JA, Miller TM, Vijayakumar V, et al. CK-2127107 amplifies skeletal muscle response to nerve activation in humans. *Muscle Nerve* 2018; **57**(5): 729–34.
119. Angelini C, Martignago S, Bisciglia M. New treatments for myasthenia: a focus on antisense oligonucleotides. *Drug Des Devel Ther* 2013; **7**: 13–7.
120. Brenner T, Hamra-Amitay Y, Evron T, Boneva N, Seidman S, Soreq H. The role of readthrough acetylcholinesterase in the pathophysiology of myasthenia gravis. *Faseb j* 2003; **17**(2): 214–22.
121. Brenner T, Hamra-Amitay Y, Evron T, Boneva N, Seidman S, Soreq H. The role of readthrough acetylcholinesterase in the pathophysiology of myasthenia gravis. *The FASEB Journal* 2003; **17**(2): 214–22.
122. Sussman J, Argov Z, Wirguin Y, Apolski S, Milic-Rasic V, Soreq H. Further developments with antisense treatment for myasthenia gravis. *Ann N Y Acad Sci* 2012; **1275**: 13–6.
123. Walker MB. Case showing the Effect of Prostigmin on Myasthenia Gravis. *Proc R Soc Med* 1935; **28**(6): 759–61.
124. Beekman R, Kuks JB, Oosterhuis HJ. Myasthenia gravis: diagnosis and follow-up of 100 consecutive patients. *J Neurol* 1997; **244**(2): 112–8.
125. CBG. Summary of Product Characteristics: Pyridostigmine. 29 oktober 2020 1990 (accessed 16-06-2021).
126. Hatanaka Y, Hemmi S, Morgan MB, et al. Nonresponsiveness to anticholinesterase agents in patients with MuSK-antibody-positive MG. *Neurology* 2005; **65**(9): 1508–9.
127. Sanders DB, El-Salem K, Massey JM, McConville J, Vincent A. Clinical aspects of MuSK antibody positive seronegative MG. *Neurology* 2003; **60**(12): 1978–80.

128. Evoli A, Tonali PA, Padua L, et al. Clinical correlates with anti-MuSK antibodies in generalized seronegative myasthenia gravis. *Brain* 2003; **126**(Pt 10): 2304–11.
129. Suh J, Goldstein JM, Nowak RJ. Clinical characteristics of refractory myasthenia gravis patients. *Yale J Biol Med* 2013; **86**(2): 255–60.
130. Engel-Nitz NM, Boscoe A, Wolbeck R, Johnson J, Silvestri NJ. Burden of illness in patients with treatment refractory myasthenia gravis. *Muscle Nerve* 2018.
131. Thomsen JLS, Vinge L, Harbo T, Andersen H. Gender differences in clinical outcomes in myasthenia gravis: A prospective cohort study. *Muscle Nerve* 2021; **64**(5): 538–44.
132. Whitley H, Lindsey W. Sex-based differences in drug activity. *Am Fam Physician* 2009; **80**(11): 1254–8.
133. Farkouh A, Riedl T, Gottardi R, Czejka M, Kautzky-Willer A. Sex-Related Differences in Pharmacokinetics and Pharmacodynamics of Frequently Prescribed Drugs: A Review of the Literature. *Adv Ther* 2020; **37**(2): 644–55.
134. Barsky AJ, Saintfort R, Rogers MP, Borus JF. Nonspecific medication side effects and the nocebo phenomenon. *JAMA* 2002; **287**(5): 622–7.
135. Ruiter AM, Verschuuren J, Tannemaat MR. Fatigue in patients with myasthenia gravis. A systematic review of the literature. *Neuromuscul Disord* 2020; **30**(8): 631–9.
136. Ruiter AM, Verschuuren J, Tannemaat MR. Prevalence and associated factors of fatigue in autoimmune myasthenia gravis. *Neuromuscul Disord* 2021; **31**(7): 612–21.
137. Kupersmith MJ, Ying G. Ocular motor dysfunction and ptosis in ocular myasthenia gravis: effects of treatment. *Br J Ophthalmol* 2005; **89**(10): 1330–4.
138. Schlezinger NS, Fairfax WA. Evaluation of ocular signs and symptoms in myasthenia gravis. *Arch Ophthalmol* 1959; **62**: 985–90.
139. Evoli A, Tonali P, Bartoccioni E, Lo Monaco M. Ocular myasthenia: diagnostic and therapeutic problems. *Acta Neurol Scand* 1988; **77**(1): 31–5.
140. Oosterhuis HJ. The ocular signs and symptoms of myasthenia gravis. *Doc Ophthalmol* 1982; **52**(3-4): 363–78.
141. Al-Haidar M, Benatar M, Kaminski HJ. Ocular Myasthenia. *Neurol Clin* 2018; **36**(2): 241–51.
142. Lorenzoni PJ, Kay CSK, Ducci RD, Fustes OJH, Werneck LC, Scola RH. Celebrating the 70 years of pyridostigmine on therapy of Myasthenia Gravis: historical aspects of the preliminary trials. *Arg Neuropsychiatr* 2020; **78**(3): 179–81.
143. Punga AR, Stalberg E. Acetylcholinesterase inhibitors in MG: to be or not to be? *Muscle Nerve* 2009; **39**(6): 724–8.
144. Lien PW, Joshi M, Tice JA, et al. Cost-effectiveness of eculizumab and efgartigimod for the treatment of anti-acetylcholine receptor antibody-positive generalized myasthenia gravis. *J Manag Care Spec Pharm* 2024; **30**(6): 517–27.
145. Tice JA, Touchette DR, Lien PW, Agboola F, Nikitin D, Pearson SD. The effectiveness and value of eculizumab and efgartigimod for generalized myasthenia gravis. *J Manag Care Spec Pharm* 2022; **28**(1): 119–24.
146. CADTH Common Drug Reviews. Pharmacoeconomic Report: Eculizumab (Soliris): Alexion Pharma Canada Corporation: Indication: Adult patients with generalized Myasthenia Gravis. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health Copyright © 2020 Canadian Agency for Drugs and Technologies in Health.; 2020.
147. Jaretzki A, 3rd, Barohn RJ, Ernstoff RM, et al. Myasthenia gravis: recommendations for clinical research standards. Task Force of the Medical Scientific Advisory Board of the Myasthenia Gravis Foundation of America. *Neurology* 2000; **55**(1): 16–23.
148. Barnett C, Bril V, Kapral M, Kulkarni A, Davis AM. Development and validation of the Myasthenia Gravis Impairment Index. *Neurology* 2016; **87**(9): 879–86.
149. Wolfe GI, Herbelin L, Nations SP, Foster B, Bryan WW, Barohn RJ. Myasthenia gravis activities of daily living profile. *Neurology* 1999; **52**(7): 1487–9.
150. Barohn RJ, McIntire D, Herbelin L, Wolfe GI, Nations S, Bryan WW. Reliability testing of the quantitative myasthenia gravis score. *Ann N Y Acad Sci* 1998; **841**: 769–72.
151. Burns TM, Sadjadi R, Utsugisawa K, et al. International clinimetric evaluation of the MG-QOL15, resulting in slight revision and subsequent validation of the MG-QOL15r. *Muscle Nerve* 2016; **54**(6): 1015–22.
152. Atkinson MJ, Sinha A, Hass SL, et al. Validation of a general measure of treatment satisfaction, the

- Treatment Satisfaction Questionnaire for Medication (TSQM), using a national panel study of chronic disease. *Health Qual Life Outcomes* 2004; **2**: 12.
153. Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Qual Life Res* 2011; **20**(10): 1727–36.
 154. iMTA Productivity and Health Research Group. Manual iMTA Medical Cost Questionnaire (iMCQ). Rotterdam: iMTA, Erasmus University Rotterdam, 2018.
 155. Bouwmans C, Krol M, Severens H, Koopmanschap M, Brouwer W, Hakkaart-van Roijen L. The iMTA Productivity Cost Questionnaire: A Standardized Instrument for Measuring and Valuing Health-Related Productivity Losses. *Value Health* 2015; **18**(6): 753–8.
 156. Barnett C, Bril V, Kapral M, Kulkarni AV, Davis AM. Myasthenia Gravis Impairment Index: Responsiveness, meaningful change, and relative efficiency. *Neurology* 2017; **89**(23): 2357–64.
 157. Muppidi S, Wolfe GI, Conaway M, Burns TM. MG-ADL: still a relevant outcome measure. *Muscle Nerve* 2011; **44**(5): 727–31.
 158. Versteegh MM, Vermeulen KM, Evers SMAA, de Wit GA, Prenger R, Stolk AE. Dutch Tariff for the Five-Level Version of EQ-5D. *Value Health* 2016; **19**(4): 343–52.
 159. Stiggelbout AM, Eijkemans MJ, Kiebert GM, Kievit J, Leer JW, De Haes HJ. The 'utility' of the visual analog scale in medical decision making and technology assessment. Is it an alternative to the time trade-off? *Int J Technol Assess Health Care* 1996; **12**(2): 291–8.
 160. Guideline for economic evaluations in healthcare: National Health Care Institute Netherlands, 2024.
 161. Zorginstituut Nederland. medicijnkosten.nl. <https://www.medicijnkosten.nl/> (accessed May 2024).
 162. Zwaap J KS, Van der Meijden C, Staal P, van der Heiden L. Cost-effectiveness in practice Diemen: Zorginstituut Nederland, 2015.
 163. de Meel RHP, Barnett C, Bril V, Tannemaat MR, Verschuuren J. Myasthenia Gravis Impairment Index: Sensitivity for Change in Generalized Muscle Weakness. *J Neuromuscul Dis* 2020; **7**(3): 297–300.
 164. Pasqualin F, Barnett C, Guidoni SV, Albertini E, Ermani M, Bonifati DM. Validation of the Italian version of the Myasthenia Gravis Impairment Index (MGII). *Neurological Sciences* 2021.
 165. Katzberg HD, Barnett C, Merkies IS, Bril V. Minimal clinically important difference in myasthenia gravis: outcomes from a randomized trial. *Muscle Nerve* 2014; **49**(5): 661–5.
 166. Skov M, Ruijs TQ, Grønnebak TS, et al. The CIC-1 chloride channel inhibitor NMD670 improves skeletal muscle function in rat models and patients with myasthenia gravis. *Science Translational Medicine* 2024; **16**(739): eadk9109.
 167. Narayanaswami P, Sanders DB, Wolfe G, et al. International Consensus Guidance for Management of Myasthenia Gravis: 2020 Update. *Neurology* 2021; **96**(3): 114–22.
 168. Sullivan PW, Ghushchyan VH, Globe G, Sucher B. Health-related quality of life associated with systemic corticosteroids. *Qual Life Res* 2017; **26**(4): 1037–58.
 169. Rowland LP. Controversies about the treatment of myasthenia gravis. *J Neurol Neurosurg Psychiatry* 1980; **43**(7): 644–59.
 170. Zhang N, Hong D, Ouyang T, et al. 3,4-diaminopyridine treatment for Lambert-Eaton myasthenic syndrome in adults: a meta-analysis of randomized controlled trials. *BMC Neurol* 2021; **21**(1): 371.
 171. Ohno K, Ohkawara B, Shen XM, Selcen D, Engel AG. Clinical and Pathologic Features of Congenital Myasthenic Syndromes Caused by 35 Genes-A Comprehensive Review. *Int J Mol Sci* 2023; **24**(4).
 172. Molgó J, Lundh H, Thesleff S. Potency of 3,4-diaminopyridine and 4-aminopyridine on mammalian neuromuscular transmission and the effect of pH changes. *Eur J Pharmacol* 1980; **61**(1): 25–34.
 173. Thomsen RH, Wilson DF. Effects of 4-aminopyridine and 3,4-diaminopyridine on transmitter release at the neuromuscular junction. *J Pharmacol Exp Ther* 1983; **227**(1): 260–5.
 174. Ceccanti M, Libonati L, Ruffolo G, et al. Effects of 3,4-diaminopyridine on myasthenia gravis: Preliminary results of an open-label study. *Front Pharmacol* 2022; **13**: 982434.
 175. EMA EMA. ICH guideline M10 on bioanalytical method validation - Step 5 Reference Number: EMA/CHMP/ICH/172948/2019. 2023. https://www.ema.europa.eu/en/documents/scientific-guideline/ich-guideline-m10-bioanalytical-method-validation-step-5_en.pdf.
 176. Tannemaat MR, Verschuuren J. Emerging therapies for autoimmune myasthenia gravis: Towards treatment without corticosteroids. *Neuromuscul Disord* 2020; **30**(2): 111–9.
 177. Rice JB, White AG, Scarpatti LM, Wan G, Nelson WW. Long-term Systemic Corticosteroid Exposure: A Systematic Literature Review. *Clin Ther* 2017; **39**(11): 2216–29.

178. Bril V, Berkowicz T, Szczudlik A, et al. Efficacy and safety of maintenance intravenous immunoglobulin in generalized myasthenia gravis patients with acetylcholine receptor antibodies: A multicenter, double-blind, placebo-controlled trial. *Muscle Nerve* 2025; **71**(1): 43–54.
179. Bonar K, Boudiaf N, Zaremba P, Tarancón T, Zhou J, Jacob S. Disease burden, healthcare resource utilisation, and treatment patterns in patients with newly diagnosed myasthenia gravis in England: A retrospective cohort study. *J Neuromuscul Dis* 2025; **12**(1): 22143602241308194.
180. Antonini G, Habetswallner F, Inghilleri M, et al. Real world study on prevalence, treatment and economic burden of myasthenia gravis in Italy. *Heliyon* 2023; **9**(6): e16367.
181. Cortés-Vicente E, Álvarez-Velasco R, Segovia S, et al. Clinical and therapeutic features of myasthenia gravis in adults based on age at onset. *Neurology* 2020; **94**(11): e1171–e80.
182. Mantegazza R, Antozzi C. When myasthenia gravis is deemed refractory: clinical signposts and treatment strategies. *Ther Adv Neurol Disord* 2018; **11**: 1756285617749134.
183. Mevius A, Jöres L, Biskup J, et al. Epidemiology and treatment of myasthenia gravis: a retrospective study using a large insurance claims dataset in Germany. *Neuromuscular Disorders* 2023; **33**(4): 324–33.
184. Attarian S, Camdessanche JP, Echaniz-Laguna A, et al. Tracking myasthenia gravis severity over time: Insights from the French health insurance claims database. *Eur J Neurol* 2025; **32**(1): e16518.
185. Nelke C, Spatola M, Schroeter CB, Wiendl H, Lünemann JD. Neonatal Fc Receptor-Targeted Therapies in Neurology. *Neurotherapeutics* 2022; **19**(3): 729–40.
186. Pyzik M, Sand KMK, Hubbard JJ, Andersen JT, Sandlie I, Blumberg RS. The Neonatal Fc Receptor (FcRn): A Misnomer? *Front Immunol* 2019; **10**: 1540.
187. Howard J, Bril V, Vu T, et al. Long-term Safety and Efficacy of Efgartigimod in Patients With Generalized Myasthenia Gravis: Interim Results of the ADAPT plus Study. *Neurology* 2022; **99**(23): S37–S8.
188. Drachman DB, Adams RN, Hu R, Jones RJ, Brodsky RA. Rebooting the Immune System with High-Dose Cyclophosphamide for Treatment of Refractory Myasthenia Gravis. *Annals of the New York Academy of Sciences* 2008; **1132**(1): 305–14.
189. Mantegazza R, Antozzi C. When myasthenia gravis is deemed refractory: clinical signposts and treatment strategies. *Therapeutic Advances in Neurological Disorders* 2018; **11**: 1756285617749134.
190. Silvestri NJ, Wolfe GI. Treatment-Refractory Myasthenia Gravis. *Journal of Clinical Neuromuscular Disease* 2014; **15**(4): 167–78.
191. Thomsen JLS, Andersen H. Outcome Measures in Clinical Trials of Patients With Myasthenia Gravis. *Front Neurol* 2020; **11**: 596382.
192. C. Rozsa FS, J. De Bleecker, J. Verschuuren, S. Hoffmann, T. Vu, V. Bril, H. Murai, E. Brauer, R. Kerstens, S. Steeland, P. Ulrichs, N. Goyal, J. Vissing, R. Mantegazza, J. Howard. ePosters: Efgartigimod Demonstrates Consistent Improvements in Patients With gMG Regardless of Prior Treatment Failures. *European Journal of Neurology* 2023; **30**(S1): 543–648.
193. Hughes BW, Kusner LL, Kaminski HJ. Molecular architecture of the neuromuscular junction. *Muscle Nerve* 2006; **33**(4): 445–61.
194. Koshi EJ, Young K, Mostales JC, Vo KB, Burgess LP. Complications of Corticosteroid Therapy: A Comprehensive Literature Review. *J Pharm Technol* 2022; **38**(6): 360–7.





Appendices

Nederlandse samenvatting

List of publications

Dankwoord

Curriculum vitae