Corticosteroids in Generalized Autoimmune Myasthenia Gravis: A Narrative Review

Tarek Sharshar[1], Aurélien Mazeraud[1], Simone Birnbaum[2]

[1] Anaesthesiology and ICU department, GHU-Psychiatry & Neurosciences, Sainte-Anne Hospital, Université Paris Cité, Institute of Psychiatry and Neurosciences of Paris, INSERM U1266, Paris, France
[2] Neuromuscular Physiology and Evaluation Laboratory, Neuromuscular Investigation Center, Institute of Myology, Pitié-Salpêtrière University Hospital, Paris, France.

Corticosteroids are usually considered for treatment of patients with moderate (*i.e.* class III of the Myasthenia Gravis Foundation America (MGFA) classification), severe (i.e. Class IV), or mechanically ventilated (i.e. Class V)(1) generalized autoimmune myasthenia gravis (MG) that is not controlled by cholinesterase inhibitors (i.e. pyridostigmine)(2, 3). It is usually recommended to ombine prednisone with an immunosuppressant(2, 3), as prednisone will allow relatively rapid control of MG, and the immunosuppressant will allow prednisone tapering without destabilizing the MG. About 80% of individuals with MG are responsive to prednisone(4), irrespective of age and time from MG onset. Prednisone tapering is necessary to avoid corticosteroid side-effects, which are reported in up to 65% of cases (4) depending on its cumulative dose(5). Patients with MG develop Cushingoid symptoms in 30% of patients; weight gain, diabetes, or hypertension in 15%; and bone fracture in 5%(6). Therefore, if the Scylla of prednisone tapering is MG exacerbation, its Charybdis is side effects from continued long-term use. The therapeutic importance of prednisone tapering is supported by the fact that cumulative or final doses of corticosteroids have been considered the primary endpoint of major clinical trials along with MG clinical control(7–11). Rationally, discontinuation of steroids depends on the tapering regimens and on the efficiency of the associated immunosuppressive agent.

There are various means of administering prednisone(12). The most common method proposed in the literature consists of gradually increasing the dose up to 0.75 mg/kg on alternate days and progressively reducing it when the minimal-manifestation status (MMS) is reached(7, 13). Therefore, this increase/tapering strategy was used in two cornerstone randomized controlled trials in which high and prolonged corticosteroid treatment were reported (30 and 20 mg, at 15 and 36 months) (7, 13). Historically, this tapering regimen was initially developed for the trial on the benefit of Azathioprine (13), in 1992, and it was used much later in the thymectomy trial, in 2016(7). We have conducted the multicenter single-blind randomized MYACOR trial to determine whether faster tapering could be achieved in azathioprine-treated generalized MG in comparison with the referent tapering regimen(14) (Table 1). Our rapid-tapering regimen consisted of immediate high-doses of prednisone, daily intake but also rapid or slow-decrease when MMS or improvement was attained (Table 1). MMS attainment without prednisone at 12 months and without relapse or prednisone reintroduction at 15 months was the primary outcome. We found that the proportion of patients who met the primary endpoint was higher in the rapid than in the referent-tapering arm (39 % *versus* 9%) presenting a risk ratio of 3.61 (95% IC [1.64-7.97], $P<0.0001$), after adjusting for center and thymectomy. The reduction of the cumulative dose was 1828 mg (95% CI, -3121 to -461 mg), which corresponds to a clinically relevant sparing of 5 mg per day. Such sparing is particularly important when the daily dosage falls below 20 mg, which is a turning point in our experience with prednisone tapering. The MYACOR trial provided two other interesting findings. First, the rate of serious adverse events (SAEs) was twofold lower than previously reported (6) and did not differ statistically between the two regimens. Infection (10%), diabetes (5%), and osteoporosis (2%) were the most frequent side effects. This indicates that prevention of prednisone side effects has dramatically improved within the last three decades. Second, azathioprine was more efficient than previously reported(13). In the trial by Palace and colleagues, this reduction was not apparent until the eighteenth month and did not become significant prior to the thirty-sixth(13). More than fifty percent of participants were still treated with corticosteroids after one year(15). Since the patients' characteristics and administration of azathioprine were comparable, only the faster tapering of prednisone in the MYACOR trial can account for such a corticosteroid-sparing effect of azathioprine.

The corticosteroid-sparing effect has been assessed with other immunomodulating interventions other than azathioprine. Because it has always been tested against placebo and because of the methodological discrepancies between trials, their corticosteroid-sparing potential cannot be specified. The MGTX trial(7) demonstrated that thymectomy significantly reduced the dose of prednisone at three years, with an average alternate-day prednisone dose of 32 mg (i.e., 16 mg/day). This remaining high dose of prednisone can result from the fact that its tapering was too slow but also from the fact that only 17% of the thymectomized patients had been treated with azathioprine.

Table 1
Tapering regimens

Prednisone	**Slow-tapering regimen**	**Rapid-tapering regimen**
Initial dose	Started 10 mg, then increased by increments of 10 mg every two days up to 1.5 mg/kg (without exceeding 100 mg)	Immediately started at 0.75 mg/kg/day (without exceeding 100 mg)
Intake	Alternate Day	Daily
Tapering criteria	MMS	1) MMS 2) Improvement status
Tapering protocol	1) **<u>If MMS reached</u>** : reduction by 10 mg every 2 weeks until 40 mg, then reduction by 5 mg every month until 0 mg 2) **<u>If MMS not maintained</u>** increase by 10 mg every 2 weeks until MMS , and then tapering as described in 1)	1) **MMS reached at one month :** reduction by 0.1mg/kg every 10 days until 0.45 mg/kg/day, then 0.05 mg/kg every 10 days until 0.25 mg/kg/day, then in decrements of 1 mg every 7 to 15 days 2) **Improved status at one month :** decrease by 0.1 mg/kg every 20 days until 0.45 mg/kg/day then 0.05 mg/kg every 20 days until 0.25 mg/kg/day then 1 mg per kg every 7 to 15 days If <u>MMS is achieved</u>, then tapering is similar to sequence 1). 3) **If MMS and improvement not reached** 0.75 mg/kg maintained for the first 3 months, followed by decrease of 0.1 mg/kg every 20 days until 0.45 mg/kg/day, then by 0.05 mg/kg every 20 days until 0.25 mg/kg/day at 20 days. No further reduction. If <u>improvement is attained</u>, the tapering follows the sequence described in 2)
Severe Side-effects	can be decreased as described in 1)	can be decreased as described in 1)
MG exacerbations	1) Severe: prednisone is doubled 2) Moderate: increase to the previous dose 3) ± IvIg and PE	1) Severe: prednisone is doubled 2) Moderate: increase to the previous dose 3) ± IvIg and PE

Abbreviations : MMS : minimal manifestation status ; IvIg : intravenous immunoglobulins ; PE : plasma exchange

Using the slow-tapering regimen, a very recent open-labeled, randomized trial showed that the 15 month-cumulative dose of prednisone was significantly lower in patients with generalized MG treated with methotrexate(11). Mycophenolate mofetil (MMF) treatment was not superior to placebo in maintaining MG control during a 36-week schedule of prednisone tapering(16). Cyclosporine has also been shown to stabilize MG and to significantly reduce prednisone dosage(17). The corticosteroid-sparing effect of cyclophosphamide has not been reliably assessed, to our knowledge. It must be emphasized that cyclophosphamide, methotrexate, and cyclosporine are usually considered a therapeutic option in refractory MG, although calcineurin inhibitors are considered to be first-line immunosuppressive agents in Japan. It is too early to anticipate how new monoclonal antibody therapies will challenge the position of azathioprine and MMF as first-line immunosuppressants. The cost of these new therapies could preclude their use in a large number of countries.

The corticosteroid-sparing effect of rituximab was initially supported by a retrospective cohort study(18), then recently assessed in two placebo-controlled double-blind randomized trials (i.e. BeatMG Study and RINOMAX trial), with contradictory conclusions(8, 9). The BeatMG study showed that rituximab does not significantly increase the proportion of patients who achieve at least a 75% reduction in prednisone dose at 12 months, with tapering being gradually carried out after 8 weeks but only after confirming that MG symptoms were at least stabilized(9). The RINOMAX trial (8) reported that a single dose of rituximab increased the probability of minimal MG manifestation with less than 10 mg of prednisone at 4 months, given that prednisone was recommended to be reduced up to 8 mg/day at two months. Anti-MuSK MG might be more responsive to rituximab, notably in terms of corticosteroid-sparing(19).

In recent decades, double-blind randomized clinical trials against placebo have shown that new therapies that target complement (i.e., Eculizumab and Zilucoplan) or the neonatal-FC receptor (i.e., Efgartigimod, Batoclimab, and Rozanolixizumab) are effective in controlling MG(10, 20–22). However, the corticosteroid -sparing effect has not been assessed in any of these trials, as prednisone tapering was not allowed during the study period. Finally, intravenous immunoglobulins are not more effective than placebo in reducing corticosteroid dose by 50% at 10 months in adult patients with generalized MG(10).

In conclusion, tapering of prednisone remains a challenge in the therapeutic management of patients with generalized MG, as it is an effective treatment but associated with multiple side effects that prompts determination of its minimal effective dose as soon as possible. Azathioprine and rituximab allow rapid tapering. The corticosteroid-sparing effect of newer therapies must be assessed and compared to azathioprine and rituximab. Given their effect on MG status, it is conceivable that these new treatments will enable a dramatic reduction or even complete discontinuation of corticosteroids. On the other hand, one may argue that treatment with azathioprine and prednisone is effective and well-tolerated in the majority of patients with generalized MG, and also not expensive. Only a clinical trial will determine which immunosuppressant is the most clinically and corticosteroid-sparing agent.

References

1. Jaretzki A, Barohn RJ, Ernstoff RM, Kaminski HJ, Keesey JC, Penn AS, *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;55:16–23.

2. Gilhus NE, Verschuuren JJ. Myasthenia gravis: subgroup classification and therapeutic strategies. *Lancet Neurol* 2015;14:1023–1036.

3. Sanders DB, Wolfe GI, Benatar M, Evoli A, Gilhus NE, Illa I, *et al.* International consensus guidance for management of myasthenia gravis: Executive summary. *Neurology* 2016;87:419–425.

4. Evoli A, Batocchi AP, Palmisani MT, Monaco ML, Tonali P. Long-Term Results of Corticosteroid Therapy in Patients with Myasthenia Gravis. *ENE* 1992;32:37–43.

5. Van Staa TP, Leufkens HG, Abenhaim L, Zhang B, Cooper C. Use of oral corticosteroids and risk of fractures. *J Bone Miner Res* 2000;15:993–1000.

6. Pascuzzi RM, Coslett HB, Johns TR. Long-term corticosteroid treatment of myasthenia gravis: report of 116 patients. *Ann Neurol* 1984;15:291–298.

7. Wolfe GI, Kaminski HJ, Aban IB, Minisman G, Kuo H-C, Marx A, *et al.* Randomized Trial of Thymectomy in Myasthenia Gravis. *New England Journal of Medicine* 2016;375:511–522.

8. Piehl F, Eriksson-Dufva A, Budzianowska A, Feresiadou A, Hansson W, Hietala MA, *et al.* Efficacy and Safety of Rituximab for New-Onset Generalized Myasthenia Gravis: The RINOMAX Randomized Clinical Trial. *JAMA Neurology* 2022;79:1105–1112.

9. Nowak RJ, Coffey CS, Goldstein JM, Dimachkie MM, Benatar M, Kissel JT, *et al.* Phase 2 Trial of Rituximab in Acetylcholine Receptor Antibody-Positive Generalized Myasthenia Gravis: The BeatMG Study. *Neurology* 2021;98:e376-389.

10. Bril V, Szczudlik A, Vaitkus A, Rozsa C, Kostera-Pruszczyk A, Hon P, *et al.* Randomized Double-Blind Placebo-Controlled Trial of the Corticosteroid-Sparing Effects of Immunoglobulin in Myasthenia Gravis. *Neurology* 2023;100:e671–e682.

11. Di L, Shen F, Wen X, Lu Y, Zhu W, Wang M, *et al.* A Randomized Open-Labeled Trial of Methotrexate as a Steroid-Sparing Agent for Patients With Generalized Myasthenia Gravis. *Frontiers in Immunology* 2022;13:.

12. Farmakidis C, Pasnoor M, Dimachkie MM, Barohn RJ. Treatment of Myasthenia Gravis. *Neurol Clin* 2018;36:311–337.

13. 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;50:1778–1783.

14. Sharshar T, Porcher R, Demeret S, Tranchant C, Gueguen A, Eymard B, *et al.* Comparison of Corticosteroid Tapering Regimens in Myasthenia Gravis: A Randomized Clinical Trial. *JAMA Neurol* 2021;78:426–433.

15. Richman DP, Agius MA. Treatment of autoimmune myasthenia gravis. *Neurology* 2003;61:1652–1661.

16. Sanders DB, Hart IK, Mantegazza R, Shukla SS, Siddiqi ZA, De Baets MHV, *et al.* An international, phase III, randomized trial of mycophenolate mofetil in myasthenia gravis. *Neurology* 2008;71:400–406.

17. Tindall RSA, Rollins JA, Phillips JT, Greenlee RG, Wells L, Belendiuk G. Preliminary Results of a Double-Blind, Randomized, Placebo-Controlled Trial of Cyclosporine in Myasthenia Gravis. *New England Journal of Medicine* 1987;316:719–724.

18. Brauner S, Eriksson-Dufva A, Hietala MA, Frisell T, Press R, Piehl F. Comparison Between Rituximab Treatment for New-Onset Generalized Myasthenia Gravis and Refractory Generalized Myasthenia Gravis. *JAMA Neurol* 2020;77:974–981.

19. Hehir MK, Hobson-Webb LD, Benatar M, Barnett C, Silvestri NJ, Howard JF, *et al.* Rituximab as treatment for anti-MuSK myasthenia gravis: Multicenter blinded prospective review. *Neurology* 2017;89:1069–1077.

20. Howard JF, Utsugisawa K, Benatar M, Murai H, Barohn RJ, Illa I, *et al.* Safety and efficacy of eculizumab in anti-acetylcholine receptor antibody-positive refractory generalised myasthenia gravis (REGAIN): a phase 3, randomised, double-blind, placebo-controlled, multicentre study. *Lancet Neurol* 2017;16:976–986.

21. Howard JF, Bril V, Vu T, Karam C, Peric S, Margania T, *et al.* Safety, efficacy, and tolerability of efgartigimod in patients with generalised myasthenia gravis (ADAPT): a multicentre, randomised, placebo-controlled, phase 3 trial. *Lancet Neurol* 2021;20:526–536.

22. Yan C, Duan R-S, Yang H, Li H-F, Zou Z, Zhang H, *et al.* Therapeutic Effects of Batoclimab in Chinese Patients with Generalized Myasthenia Gravis: A Double-Blinded, Randomized, Placebo-Controlled Phase II Study. *Neurol Ther* 2022;11:815–834.