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Gender differences in prednisone adverse effects

Survey result from the MG registry

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Abstract

Objective

Prednisone is a first-line immunosuppressive treatment for myasthenia gravis (MG), whereas short-term and long-term adverse effects (AEs) are a limiting factor in its usage.

Method

The MG patient registry is a patient-driven, nation-wide database with patients of age ≥18 years, who were diagnosed with MG and live in the United States. Custom-designed "prednisone-steroid use and MG" survey was sent out to MG registry participants as part of semi-annual follow-up. Data were collected and analyzed for frequency.

Results

A total of 398 MG participants (21% response rate) completed the survey, including 173 men and 225 women. Among them, 298 reported current (174) or past (288) prednisone intake. Current prednisone dosage varied from 0.5 to 75 mg (median 10 mg, IQR 7–20), dosing frequency was daily in 132 (76%) and every other day in 31 (18%). Peak prednisone dose was commonly between 25 mg and 60 mg (Median 50 mg, IQR 25–60); however, doses more than 60 mg daily were reported in 59 (20%). Prednisone AEs were reported more commonly in women (95% vs 81%, $p < 0.0001$). Women reported more intolerable AEs (77% vs 50%, $p < 0.00001$) and less willingness to accept a dose increase (26% vs 44%, $p = 0.03$) compared with men.

Conclusions

Prednisone is commonly used in the treatment of MG, with highly variable dosages and dosing frequencies reflecting the absence of a standard guideline. Intolerable AEs were more commonly reported among women and was associated with unwillingness to accept a dose increase. Consensus guidelines and their validation are required to guide prednisone treatment for MG.

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Glossary

AE = adverse effect; **ICU** = intensive care unit; **IRB** = institutional review board; **IVIG** = IV immunoglobulin treatment; **MG** = myasthenia gravis; **PLEX** = current plasma exchange; **UAB** = University of Alabama at Birmingham.

Prednisone has been shown to be effective in treating myasthenia gravis (MG) and is currently used as a first-line immunosuppressive therapy.[1–6] The use of prednisone, however, is often limited because of the numerous short- and long-term adverse effects (AEs) associated with its glucocorticoid and mineralocorticoid activities. These AEs tend to increase with higher doses, more frequent dosing, and prolonged treatment period.[7–13] The frequency of steroid AEs has been reported in up to 67% of treated populations[2,3] and is likely underestimated. Clinicians are concerned of serious AEs such as osteoporosis-related fracture, aseptic necrosis, infection, and gastrointestinal bleeding. AEs that are clinically considered "benign" can still be disturbing from the patient's perspective and might lead to the request of dose reduction or poor compliance. Tapering the dose of prednisone while maintaining disease control has become a treatment goal in MG care and an important end point in MG clinical trials.[14–16]

Recent analyses from the MG patient registry showed that women were less likely to be on current prednisone treatment despite having worse disease severity ratings compared with men.[17] We suspect that this observation is due to gender differences in the frequency or tolerability of steroid AEs; however, we found no studies that systemically evaluated this hypothesis in the MG population. Therefore, we designed a survey of MG registry participants regarding AEs and personal beliefs governing the use of prednisone to delineate potential gender effects on the perception of prednisone AEs.

Methods

The MG patient registry is a database managed by the Myasthenia Gravis Foundation of America and the coordinating center at the University of Alabama at Birmingham (UAB), with oversight by the UAB Institutional Review Board (IRB). Details of the registry, registry participants, mode of data collection, and collected participant-reported outcome measures were described in the previous study.[17]

We composed a Prednisone-Steroid use and MG Survey (Prednisone Survey), which included 11 questions asking the participants about the status of prednisone use, current and highest doses and frequencies, AEs experienced, and willingness to increase steroid dose for better disease control. The 33 items included in the AEs list were derived from MGTX treatment-associated symptoms and treatment-associated complications.[14] Participants were asked to select AEs they experienced from taking steroid (prednisone) and select them once more if any of them were difficult to tolerate (appendix e-1, links.lww.com/NXI/A77). This survey was sent to the MG registry participants along with the semi-annual follow-up for those who enrolled before April 15, 2017.

Inclusion and exclusion criteria

Patients age ≥18 years who answered "Yes" to "Has your doctor diagnosed you with MG?", resided in the United States, and completed the 9th semi-annual follow-up survey before November 29, 2017 were included.

Statistical analysis

Basic demographic, disease-related history and answers to the survey questions were compared between survey responders vs nonresponders, responder with prednisone use vs no prednisone use, male vs female responders, and responders with intolerable AEs vs no intolerable AEs. The Student *t*-test was used to compare continuous variables such as age, age at symptom onset, age at treatment onset, current dose, highest dose, treatment duration, MG quality of life 15 (MG-QOL15), and MG activity of daily living (MG-ADL) sum scores. Categorical variables such as sex, race, thymoma, thymectomy, intensive care unit (ICU) admission in the past, feeding tube in the past, current and past prednisone use, current use of immunosuppressant agents, current intravenous immunoglobulin (IVIG) treatment, and current plasma exchange (PLEX) treatment were summarized and compared using the Fisher exact test. A p value less than 0.05 was used for statistical significance without adjustments for multiple comparisons because of the exploratory nature of this article. SAS version 9.4 and programs from the R project version 3.3. 2 were used for statistical analysis.

Data availability statement

Data not provided in the article because of the space limitations will be made available in a trusted data repository or shared at the request of other investigators for purposes of replicating results.

Standard protocol approvals, registrations, and patient consents

General registry and each study and/or survey obtains approval by the UAB IRB, and consent for participation is believed to be obtained when each participant completes their survey.[17]

Results

One thousand eight hundred fifty-nine MG patient registry enrollees received the 9th semi-annual follow-up and the Prednisone Survey irrespective of whether they had ever responded to a semi-annual update after registration. Among them, 398 participants responded to the 9th semi-annual

follow-up survey and Prednisone Survey (21% response rate). When the demographics of survey responders were compared with nonresponders, survey responders were more likely to be white and older at enrollment. Among the 398 Prednisone Survey responders, 100 participants answered that they were never treated with prednisone and that the survey was ended (no-prednisone group). The remainder, 298 participants, who answered that they took prednisone (prednisone group) in the past or are currently taking prednisone completed the survey. Compared with the no-prednisone group, the prednisone group had higher (worse) MG-ADL score at enrollment, reported more frequent ICU admission, and was more likely to be receiving an immunosuppressant and IVIG treatment (table 1).

Among the 298 participants in the prednisone group, 173 (58%) were currently receiving prednisone. Peak prednisone dose was reported most commonly between 25 and 60 mg (median 50 mg, IQR 25–60); however, doses more than 60 mg daily were reported in 59 (20%). Peak dosage was daily in 249 (83%) and every other day in 18 (6%). Current prednisone dosage varied from 0.5 to 75 mg (median 10 mg, IQR 7–20). Current prednisone dosing frequency was daily in 132 (76%) and every other day in 31 (18%).

Among the survey responders who took prednisone, women were younger, younger at the age of initiation of steroid treatment, lower in weight, higher in MG-QOL15, and MG-ADL (worse) scores, and more likely to report an MG exacerbation in the past 6 months. The rate of treatment with prednisone, current prednisone treatment, current dose, highest dose, treatment duration, and dosing frequency were comparable between men and women. Women were more likely to answer that their steroid dose was lowered from the highest dose because of AEs compared with men. Women also answered "no" more frequently than men when asked "if your MG symptoms worsen, are you willing to try a dose of steroid (prednisone) higher than your current dose or to start steroid if not on it currently.?" This gender difference was not observed when asked "if your MG symptoms worsen significantly, are you willing to try your previous highest dose steroid (prednisone) or, if currently on your highest dose to increase it further?" (table 2).

Women reported prednisone AEs and intolerable AEs more commonly compared with men (95% vs 81%, 77% vs 50%, respectively). Women reported weight gain, increased appetite, changed appearance, moon face, prominent scar, increased hair loss, gingival hyperplasia, mood swing, depression, fatigue, poor concentration, headache, sleeplessness, and palpitation more commonly than men. When asked about intolerable AEs, women reported more frequently than men including weight gain, changed appearance, moon face, depression, fatigue, mood swing, increased hair loss, sleeplessness, and stomach complaints (table 3).

The group of responders who reported intolerable AEs (INTOL) were more likely to be women, younger in age, who took a higher peak dose of prednisone, and were less likely to say "yes" when asked to increase prednisone dose for worsened MG compared with the group reporting no intolerable AEs (NO INTOL) from prednisone. MG exacerbation in the past 6 months was more frequent in the group with intolerable AEs, and MG-QOL15 and MG-ADL sum scores were significantly higher (worse) compared with the no intolerable AE group (table 4).

Table 1 Comparison of the basic demographic and disease-related history between responder vs nonresponder and prednisone vs no-prednisone groups

	Responder (398)				
	Total (398)	**Prednisone (298)**	**No-Prednisone (100)**	**Nonresponder (1,461)**	***p* Value**
Sex (% F)	57%	54%	64%	64%	NS
Race (% white)	95%	95%	97%	89%	0.0019
Age at enrollment (SD)	58.7 (12.2)	58.3 (12.5)	59.8 (11.8)	53.8 (15.2)	<0.0001
Time from enrollment (y)	2.19	NA	NA	2.13	NS
ICU admission (%)	29%	33%	17%	—	0.02
Feeding tube (%)	11%	12%	7%	—	NS
Current immunosuppressant (%)	44%	47%	34%	—	0.03
Current IVIG (%)	17%	19%	10%	—	0.03
Current PLEX (%)	3.7%	3.4%	5%	—	NS
MG-ADL (SD)	5.2 (4.1)	5.5 (4.1)	4.4 (3.9)	—	0.016

Abbreviations: ICU = intensive care unit; IVIG = intravenous immunoglobulin; MG-ADL = myasthenia gravis activity of daily living; NS = not significant; PLEX = plasma exchange.

Table 2 Comparison of the basic demographic, disease-related history, Prednisone Survey results, and patient-reported outcomes between male and female survey responders

	Men	Women	*p* Value
Total	173	225	NA
Age (SD)	67 (9.8)	59 (12.5)	<0.0001
Age at treatment onset (SD)	60.9 (14.5)	50.7 (11.5)	<0.0001
Prednisone treatment (%)	79%	72%	NS
Current prednisone (%)	48%	40%	NS
Current daily dose (mg, SD)	15.3 (14.0)	13.5 (10.0)	NS
Current dose frequency (% daily)	81%	71%	NS
Treatment duration (mo, SD)	44.3 (74.6)	52.0 (85.7)	NS
Highest daily dose (mg, SD)	52.6 (29.5)	50.1 (30.2)	NS
Highest dose frequency (% daily)	82%	85%	NS
Highest dose duration (mo, SD)	3.0 (1.1)	3.1 (1.1)	NS
Dose lowered because of adverse effects	13%	27%	0.01
If MG worsens, dose increases? (% yes)	44%	26%	0.03
If MG worsens significantly, dose increases to previous highest dose? (% yes)	45%	38%	NS
MG-QOL15	14.5 (12.7)	22.4 (14.9)	<0.0001
MG-ADL	4.3 (3.6)	6.5 (4.3)	<0.0001
Exacerbation in the past 6 months (%)	22%	38%	0.015
Height (cm, SD)	176 (7)	161 (7)	<0.00001
Weight (kg, SD)	102 (25)	83 (22)	<0.00001

Abbreviations: MG-ADL = myasthenia gravis activity of daily living; MG-QOL15 = myasthenia gravis quality of life 15; NA = not applicable; NS = not significant.

Discussion

In our study, majority of the participants took prednisone for the treatment of MG, whereas a quarter answered that they did not take prednisone. Those who did not take prednisone generally had less severe disease; however, a significant proportion of these participants had severe enough disease that required immunosuppression, IVIG, or PLEX. Among participants who took prednisone, the reported prednisone usage patterns were variable in terms of dosages and dosing frequencies. Comparable peak dosage between men and women suggests that the dosing in this population is not commonly based on ideal body weight. Daily dosing was the predominant dosing frequency, especially at the peak dose (84%), despite literature that supports the use of alternate-day dosing to decrease AEs.[6,14]

As expected, reported AEs were very common among patients with MG taking oral corticosteroid treatment, consistent with the previous reports.[1–10,18] The efficacy of the corticosteroid medications such as prednisone rely on its pleiotropic effects on the glucocorticoid receptors through multiple signaling pathways, which inevitably evoke physiologic signaling along with its anti-inflammatory effect.[19] Women in this study not only reported AEs more commonly but also perceived them as more intolerable compared with men. Consistent with this result, women more frequently reported that the dosage of prednisone had to be lowered because of AEs. Experiencing intolerable AEs was associated with a tendency to be resistant to a possible future dose increase if needed for an MG exacerbation, and this was more common in women.

A previous study that looked at symptom experience associated with chronic immunosuppressive treatment in heart transplant recipients and the result showed that clear gender difference exists.[18] In the study, women reported adverse symptoms more frequently with a higher distress level, and the pattern of symptoms was different from men. Women also experienced more AEs in the MG patient registry, the MG population treated with long-term steroids. There are many potential factors that might explain this observation. Physiologically, women have lower height and weight compared with men. Considering that the mean highest and current dose of prednisone were comparable, women would generally be receiving a higher dose of prednisone on a per weight basis, which would be expected to be associated with more adverse events.

Table 3 Comparison of the reported prednisone AEs and intolerable AEs between male and female survey responders

	Men (137)	INTOL	Women (161)	INTOL	Ratio[a]	*p* Value	*p* Value (INTOL)
Any AEs?	81%		95%			<0.0001	
Any intolerable AEs?		50%		77%			<0.0001
Acne	8.0%	2.2%	12.5%	7.5%	2.2	0.3	0.06
Back pain	15.3%	5.8%	16.3%	5.0%	0.8	0.9	0.8
Bruises	32.8%	5.1%	42.5%	11.3%	1.7	0.1	0.09
Changed appearance	29.2%	6.6%	56.3%	31.9%	2.5	0.003	<0.0001
Changed taste	8.8%	2.9%	13.1%	5.0%	1.2	0.4	0.6
Decreased interest in sex	14.6%	2.2%	21.9%	6.3%	1.9	0.2	0.15
Depression	16.1%	7.3%	24.4%	18.8%	1.7	0.09	0.006
Diabetes mellitus/elevated blood sugar	19.7%	10.9%	25.0%	13.8%	1.1	0.4	0.6
Diarrhea	19.7%	6.6%	18.8%	8.1%	1.3	0.9	0.7
Fatigue	29.2%	9.5%	34.4%	19.4%	1.7	0.6	0.02
Fracture	3.6%	2.9%	8.8%	7.5%	1.1	0.1	0.1
Fragile skin	32.1%	10.9%	33.8%	10.6%	0.9	0.9	1
Gingival hyperplasia (gum swelling)	2.9%	1.5%	9.4%	0.6%	0.1	0.03	0.6
Headache	10.9%	5.8%	20.0%	11.9%	1.1	0.04	0.1
High blood pressure	20.4%	7.3%	19.4%	6.3%	0.9	0.9	0.8
Impotence/painful menstruation	2.9%	2.2%	3.1%	0.6%	0.3	1	0.3
Increased appetite	39.4%	9.5%	51.9%	16.9%	1.4	0.04	0.09
Increased hair loss	3.6%	0.7%	28.1%	8.8%	1.6	<0.0001	0.002
Inflammation	5.1%	2.2%	11.3%	5.0%	1.0	0.1	0.4
Mood swings	30.7%	11.7%	43.1%	24.4%	1.5	0.03	0.006
Moon face	27.0%	8.8%	59.4%	30.6%	1.6	<0.0001	<0.0001
Painful/inflamed/prominent scar	0.7%	0.0%	6.3%	1.9%	NA	0.03	0.3
Palpitations	8.8%	4.4%	21.3%	9.4%	0.9	0.01	0.2
Persistent chest pain	2.9%	1.5%	3.8%	1.3%	0.7	0.8	1
Poor appetite	1.5%	0.0%	5.0%	1.3%	NA	0.1	0.5
Poor concentration	10.2%	8.8%	20.6%	10.0%	0.6	0.02	0.8
Poor vision	15.3%	7.3%	16.9%	10.6%	1.3	0.9	0.4
Serious infection	5.1%	5.1%	9.4%	7.5%	0.8	0.3	0.5
Sleeplessness	31.4%	18.2%	48.1%	36.3%	1.3	0.04	0.01
Stomach complaint	16.1%	5.8%	19.4%	14.4%	2.1	0.6	0.03
Swollen ankles	24.1%	6.6%	26.9%	10.6%	1.4	0.7	0.3
Tremor	10.2%	5.1%	8.1%	3.1%	0.8	0.7	0.6
Weight gain	56.2%	25.5%	68.8%	48.8%	1.6	0.03	<0.0001
	A	B	C	D			

Abbreviations: AE = adverse event; INTOL = intolerable.
[a] Ratio: calculated by AD/BC.

Table 4 Characteristics of participants reporting intolerable prednisone AEs

	INTOL (192)	NO INTOL (106)	*p* Value
Sex (%F)	65%	35%	<0.00001
Current age (SD)	58.7 (11.6)	64.1 (12.8)	0.0004
Current prednisone (%)	61%	54%	0.5
Highest prednisone daily dose (mg, SD)	55.6 (28.9)	44.5 (30.0)	0.002
Highest dose duration (mo)	50.8 (79.3)	43.8 (83.6)	0.5
Current prednisone daily dose (mg, SD)	15.1 (12.8)	13.0 (10.4)	0.3
Exacerbation in the past 6 months (% yes)	43%	21%	0.0003
MG-QOL15	22.6 (14.2)	12.1 (12.6)	<0.00001
MG-ADL	6.4 (4.1)	3.8 (3.6)	<0.00001
If MG worsens, dose increases? (% yes)	25%	51%	<0.00001
If MG worsens significantly, dose increases to previous highest dose? (% yes)	37%	49%	0.05

Abbreviations: AE = adverse event; INTOL = group of responders who reported intolerable AEs; NO INTOL = group reporting no intolerable AEs; MG-ADL = myasthenia gravis activity of daily living; MG-QOL15 = myasthenia gravis quality of life 15.

Pharmacokinetics are different between men and women. Female sex and oral contraceptive use have been associated with lower prednisolone clearance and volume of distribution, increasing the area under the curve in healthy volunteers and kidney, lung, and heart transplant recipients.[20] Women in the MG registry generally have more severe disease compared with men,[17] which might have led to higher cumulative dosage exposure. The peak and current dosages and treatment durations were comparable between the sexes in our study; however, this may not precisely reflect the cumulative dosage of prednisone because of its highly variable titration and tapering courses.

AEs related to appearance and social interactions were significantly more likely to be intolerant in women compared with men, suggesting that the study result might have been affected by different perception of AEs between the 2 sexes. For example, altered appearance was 2.5 times more likely to be intolerable by women than men. Weight gain, acne, bruises, loss of sexual interest, depression, fatigue, increased hair loss, mood swing, moon face, weight gain, and stomach complaints all were more frequently noted as intolerable AEs in women. By contrast, factors that are neutral to social interaction such as palpitation, chest pain, poor vision, or infection were considered intolerable at similar frequencies between the sexes. This observation is not surprising because studies showed that women as a group maintain more social contacts, communicate more frequently, and strive to stay in the center of a social network.[21,22] In the same context, women are more cognizant of their visual appearance as shown by the study of the social network using Facebook, a large social network service.[22]

Experiencing AEs is known to affect quality of life and can trigger medication noncompliance.[23–26] The result from our study also demonstrates that having intolerable AEs might lead to resistance in prednisone dose increase when it is needed for MG treatment. Participants who reported intolerable AEs were more likely to be women, younger, had more severe disease, and were treated with higher peak dose of prednisone. These findings might simply indicate that those with more severe disease received higher dosages of prednisone and therefore developed intolerable AEs. Alternatively, initial high dose of prednisone challenge might have caused intolerable AEs and resistance to future prednisone treatment, leading to incomplete disease control. In the latter case, applying a strategy to avoid intolerable AEs might positively affect the patient's perception and compliance with prednisone, a potential target to improve the treatment outcome. We cannot make a cause and effect relationship based on this cross-sectional study, and a further prospective study is needed to further guide prednisone use in the treatment of MG.

Potential recall bias is one of the main limitations of our study. Most of our patients were treated with long-term prednisone, and it might be difficult to accurately remember and report various AEs they have experienced. Many of the patients were also treated with other medications including pyridostigmine, immunosuppressants, or received no MG-related medications, making it difficult for them to link certain symptoms to specific medications. We also acknowledge that there might be a gender bias in reporting, one way or another affecting the survey results. The responders of this particular survey were older and mostly white compared with nonresponders and may not reflect the whole MG patient registry population or patients with MG in the United States. The response rate for the semi-annual follow-up and Prednisone Survey was not high, reflecting the early evolution of the registry and not having a way to exclude participants who agree with registration but prefer not to participate in semi-annual updates. As pointed out in our previous study, data in the

registry are entered by the participant and did not go through confirmation by a physician. Some of the information such as the dose or duration might not be precise, as it is relying on the sole memory of the individual participant. Nonetheless, we believe that the value of our study lies in the data collected to represent the perspective of patients without significant influence from the providers. Ultimately, the final decision whether or not to take the medicine is on the patient, not the treating physician.

In summary, subjective treatment-associated AEs are extremely common in patients taking prolonged oral corticosteroids such as prednisone, more frequent in women with higher tendency for intolerance. Experiencing intolerable AEs is linked to resistance in increasing the dose of prednisone when it is needed for the treatment of underlying disease. Consensus guidelines and their validation are required to guide prednisone treatment for MG.

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Appendix 1. Author contributions

Name	Location	Role	Contribution
Ikjae Lee, MD	University of Alabama at Birmingham	Author	Design and conceptualized the study; analyzed the data; and drafted the manuscript for intellectual content
Henry J Kaminski, MD	The George Washington University	Author	Design and conceptualized the study; reviewing; and editing the manuscript for intellectual content
Tarrant McPherson, MA	University of Alabama at Birmingham	Author	Major role in the acquisition of data
Michelle Feese, MPH	University of Alabama at Birmingham	Author	Contribution in forming and distributing the survey
Gary Cutter, PhD	University of Alabama at Birmingham	Author	Design and conceptualized the study; analyzed the data; and reviewing and editing the manuscript for intellectual content