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Ocular Myasthenia Gravis: Controversies and Updates

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Abstract The majority of patients with myasthenia gravis (MG) initially present with ocular symptoms. An unresolved question is whether there are clinical features at onset to guide clinicians to predict an individual patient's conversion risk from ocular MG (OMG) to generalized disease, or "secondary generalized MG" (SGMG), that is, a prognostic model. In light of the emerging theory that early corticosteroids may have a risk-modifying effect, the factors associated with secondary SGMG previously reported should be revisited. Studies showing potential risk-modifying effects of corticosteroids are useful, though flawed, owing to the heterogeneous retrospective studies and methods of reporting. Updates on other potential immunosuppressive agents are also discussed. Thymectomy in OMG has been recently reported in a few studies to be useful. MG associated with antibodies to muscle-specific kinase, usually associated with severe generalized MG, can cause a pure OMG syndrome. Recent serological developments in seronegative patients have also revealed antibodies to clustered anti-acetylcholine receptor and lipoprotein receptor-related protein-4.

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Introduction

Myasthenia gravis (MG) is an autoimmune disease that results from defects in neuromuscular transmission. Antibodies to the acetylcholine receptor (AChR) or, less frequently, to muscle-specific kinase (MuSK), act on the postsynaptic membrane to reduce AChR numbers or function, resulting in variable weakness of the ocular, bulbar, respiratory, and limb muscles. Antibodies to low-density lipoprotein receptor-related protein-4 (LRP4) have been identified in a small number of patients without these antibodies.

MG is classified as ocular or generalized, depending on the distribution of weakness. Approximately 80 % of patients have generalized MG (GMG) and 20 % have ocular MG (OMG)[1]. OMG can result in ptosis and diplopia that some patients find very disruptive to daily activities. Table 1 illustrates the differential diagnosis of OMG. The diagnosis is primarily clinical, and supported by electrophysiology and serological detection of antibodies. With standard assays, AChR antibodies are detectable in approximately 50 % of patients with OMG and 80–85 % of patients with GMG [2]. Patients are widely treated with immunotherapies that reduce antibody levels and clinical severity.

Ocular muscles demonstrate relatively reduced safety factor and complement regulation, simplified postsynaptic structure, and increased susceptibility to toxins [3•, 4, 5]. Accordingly, in the majority of patients with MG (50–85 %), disease starts with isolated ocular symptoms [6–8]. However, typically in the first 2 years, 50–80 % of these patients will develop systemic neuromuscular weakness converting to secondary GMG (SGMG) [6, 8, 9]. For this reason, an arbitrary minimum duration of 2 years of isolated ocular symptoms is

Table 1 Differential diagnosis of ocular myasthenia gravis

Thyroid eye disease
Congenital and acquired strabismus
Chronic progressive external opthalmoplegia
Kearns–Sayre disease
Single and multiple cranial neuropathy (III, IV, VI)
Levator dehiscence
Myotonic dystrophy

considered a reasonable limit for diagnosing OMG, as the likelihood of conversion to SGMG after 2 years is rare [8]. This classification, however, is difficult to apply in practice, as many patients with OMG only are treated with immunotherapies within 2 years of onset.

This article aims to update readers on the current controversies and recent developments in OMG.

Is it Possible to Predict Conversion Risk from OMG to SGMG?

Can one predict which patients will generalize and can a prognostic model be created? Several retrospective studies have reported factors associated with SGMG [6, 8, 10–15], which include older age of onset [6], seropositivity [13], abnormal repetitive accessory nerve stimulation [15], and severity of symptoms [15]. Apart from the study by Bever et al. [6], which was designed to investigate prognostic risk for SGMG, the studies were designed to investigate the effects of corticosteroids or immunosuppression on disease outcome. Therefore, these reported associations may be misleading, that is confounded by corticosteroid use, in light of the emerging theory that early corticosteroids may have a risk-modifying effect (discussed further below). A study exploring prognostic factors in non-immunosuppressed OMG patients will avoid this confounding issue. Unfortunately, data in the above-mentioned published studies did not provide sufficient detail to allow reanalysis in the non-immunosuppressed group only.

A prognostic model that stratifies patients to "low" or "high" risk would be helpful with regard to counseling, management and selection of suitable patients for a randomized control trial of early corticosteroid treatment. Such a model has not been previously produced. We are currently performing such a study, with the aim of creating a prognostic model.

Can the Progression to GMG be Modified with Corticosteroids?

Arguably the most hotly debated issue in recent years is whether early immunosuppression with corticosteroids can reduce the risk of conversion from OMG to GMG. An inherent difficulty in answering this question is the natural evolution of OMG. About 20 % of patients, irrespective of corticosteroid treatment, will not develop SGMG [1]. Likewise, a firm diagnosis of OMG is difficult to make in the first 2 years given the high rate of conversion to SGMG. Ideally, one would select the 50–80 % who would develop SGMG and assess the protective capacity of different interventions. Unfortunately, as discussed above, there is currently no reliable distinguishing clinical or serological factor to identify these patients.

It has been more than 15 years since the possibility of modifying generalized progression from OMG was first suggested by Kupersmith et al. [16] in a retrospective case series. Subsequently, five retrospective cohort studies [12–15, 17] have replicated this observation. However, despite vigorous debate by experts [18–22], this issue remains unresolved. This is partly owing to the reasons mentioned above and the methodology of these retrospective studies. These factors and the results of the trials are summarized in Table 2.

There are several criticisms regarding these studies showing a risk-modifying effect of steroids. First, in most of the studies, the duration of symptoms before immunosuppression with corticosteroids was not clearly stated [13–17]. This is relevant as the risk of secondary generalization reduces with time; in particular, the largest drop in risk occurs after the first year following symptom onset [6, 9, 23]. The timing of immunosuppression, as well as dosage, in autoimmune disease course may also be an important factor [24]. Of note, though, Kupersmith [12] subsequently reported, in a cohort sharing many patients with that reported in 2003, that 90 % received corticosteroids within 6 months of symptom onset. The patients reported by Monsul et al. [17] were all given corticosteroids within 2 years, although the specific interval was not stated; and those reported by Mee et al. [14] most likely received corticosteroids within 2 years of symptom onset, although this was not clearly stated.

Second, conversely, some patients may have been recruited too early from onset of symptoms, that is the patients who develop GMG very early may be different from other patients with OMG. Oosterhuis [9] suggested a minimum of 3 months as the limit for purely ocular symptoms before classifying a patient as having OMG. Accordingly, Sommer et al. [15] and Monsul et al. [17] only included patients who had purely ocular symptoms for at least 3 months from symptom onset. However, studies by Kupersmith and colleagues [12, 13, 16] and Mee et al. [14] included patients who developed GMG within 3 months of symptom onset. For example, in Kupersmith's 2009 study [12], all 16 untreated patients who developed GMG did so at a mean of 2.6 months (range, 1.2–9.6); in the 2003 study by Kupersmith et al. [13], a large proportion of the untreated patients who developed GMG did so within 3 months of symptom onset; in the study by

Table 2 Summary of retrospective studies analyzing secondary generalized myasthenia gravis (MG) risk modification

Study [ref.]	Number of patients with 2-y follow up data or until conversion to GMG	Anti-AChR seropositive	Number treated with 1. Corticosteroids. 2. Azathioprine 3. Both	Symptom duration prior to corticosteroid treatment	Corticosteroid treatment regimen	FU duration	Outcome: proportion converted to GMG	Comment
Kupersmith et al. 1996 [16][a]	32	10/28	1. 32/32	Not reported	Initiation: 40–80 mg daily,	≥ 2 y	At 2 y: 3/32 (treated group)	Case series;
			2. 0		Taper: 4–6 wks		At last FU: 5/32 (treated group)	27/32 first seen at ≤2 mo from symptom onset, 5/32 at >1 y;
			3. 0		Repeat courses if flare ups			6/32 on alternate day 2.5–20.0 mg for >6 mo
Kupersmith et al. 2003 [13][a]	94	32/94	1. 58/94	Not reported	Initiation: 50–60 mg daily	≥2 y	At 2 y: 4/58 (treated group) 13/36 (untreated group)	Included children (n=6 aged 2–10 y); Included patients who developed GMG within 3 mo of symptom onset;
			2. 0		Taper: 5–8 wks	OMG patients: mean 4.6 y range: 2–16 y	At last FU: 9/58 (treated group) 15/36 (untreated group)	Relatively low proportion of seropositive patients
			3. 0					Most patients remained on daily or alternate daily dose prednisone 2.5–10.0 mg (number not specified)
Kupersmith 2009 [12][a]	87	36/87	1. 55/87	≤6 mo in 47/55	Initiation: 50–60 mg daily	Treated group mean: 7.2 y range: 2.5–20.0 y	At last FU: 7/55 (treated group) 16/32 (untreated group)	Included children aged ≥4 y; Included patients who developed GMG within 3 mo of symptom onset
			2. 0	> 1 y in 4/55	Taper: 10–12 wks	Untreated group mean: 4.6 y range: 0.1–20.0 y		For untreated patients who developed GMG, mean duration from symptom onset=2. 6 mo (range 1.2–9.6)
			3. 0		Periods of higher dosing if flare ups			Most patients continued to receive daily or alternate daily dose prednisone 2.5–10.0 mg (number not specified)
Sommer et al. 1997 [15]	78	43/66	1. 22/78	Not reported	Initiation: 10–60 mg daily (for 2–3 mo if severe)	Not specified	At last FU: 6/50 (treated group) 18/28 (untreated group)	Only included patients with ≥3 mo of ocular symptoms only from disease onset
			2. 4/78		Taper: up to 1 y			Symptom duration prior to corticosteroid likely ≥6 mo; Mean disease duration 8.3 y (range 0.5–58.2)
			3. 23/78					1/50 patients in the treated group had thymectomy (only); missing data re. anti-AChR in 12 patients
Mee et al. 2003 [14]	34	34/34	1. 6/32	Not reported	Initiation: 25 mg daily	All patients: mean 4.2 y range: 0.3–15.25 y[b]	At last FU: 2/12 (treated group) 19/22 (untreated group)	Only anti-AChR seropositive patients included
			2. 0		Taper: not stated	OMG patients: mean: 4.2 y range: 2.00–12.75 y		Included 7 patients who developed GMG within 3 mo of symptom onset
			3. 5/32			SGMG patients: mean: 4.2 y range: 0.30–15.25 y		

Table 2 (continued)

Study [ref.]	Number of patients with 2-y follow up data or until conversion to GMG	Anti-AChR seropositive	Number treated with 1. Corticosteroids. 2. Azathioprine 3. Both	Symptom duration prior to corticosteroid treatment	Corticosteroid treatment regimen	FU duration	Outcome: proportion converted to GMG	Comment
Monsul et al. 2004 [17]	56	31/56	1. 27/56	≤2 y	Initiation: 40–60 mg daily	≥ 2 y	At 2y: 3/27 (treated group) 10/29 (untreated group)	Only included patients with ≥3 mo of ocular symptoms only from disease onset
			2. 0		Taper: 3–6 mo			Majority of patients remained on prednisone 2.5–10.0 mg daily at 2 years (number not specified)
			3. 0					

At baseline, all patients were considered to have ocular MG (only); patients included if FU ≥2 y, or until first genaralized symptom (may be <2 y)

Heterogeneous studies, with different symptom duration for inclusion (see comments)

FU follow up

[a] Likely overlap of patient cohort, as similar database used

[b] Calculated from data in article

Mee et al. [14], 7/19 non-immunosuppresed patients converted to GMG within 3 months of symptom onset.

Third, there is possible selection bias in all the above studies, as treatment was not randomized.

Fourth, the treatment (immunosuppressed) and control (non-immunosuppressed) groups may not have been adequately matched for known risk factors for SGMG; and the method of reporting may not have provided the information necessary to compare patient characteristics between treatment and control groups [15]. Two studies had a larger proportion of seronegative patients in the treatment group than in the non-immunosuppressed group [12, 17]. Although the difference did not reach statistical significance, the *P*-values of 0.09 and 0.11 do raise the possibility of a confounding factor. This is of particular relevance as seronegative patients are less likely to develop SGMG (26 % seropositive versus 4 % seronegative) [15]. By contrast, in a non-randomized study, it may be reasonable to assume that milder OMG patients are less likely to receive steroids. If these patients have a reduced rate of progression to SGMG [15], this could make the perceived benefit of steroid treatment in a potentially more severe OMG group harder to detect.

Corticosteroids: Pros and Cons

Despite the healthy skepticism and concerns raised above, there is a reasonable argument for the early use of corticosteroids. In addition to the evidence from the handful of above-mentioned retrospective studies on the reduced risk of SGMG with corticosteroids [12–15, 17], there are further supportive hints from epidemiological data. In the era before immunosuppression use for OMG, a conversion rate to SGMG of over 60 % has been reported [9, 25] compared with 30 % [15] following the use of immunosuppression in OMG.

There is a suggestion that corticosteroids may have a beneficial effect independent of immunosuppression. In vitro studies on human muscle have shown that small doses of hydrocortisone or dexamethasone exposure increased the synthesis of AChR [26] and improved the organization of post-junctional synaptic folds [27], but these interesting studies have not been followed-up.

The duration of the attack on the neuromuscular junction may influence treatment response, lending further weight to early use of corticosteroids. Muscle atrophy has been observed in patients with longstanding generalized MG not receiving immunosuppressive treatment [9, 28]. Similarly, muscle atrophy can occur in ocular muscles, as we have recently shown on imaging in two patients with anti-AChR-positive GMG whose ocular symptoms responded poorly to treatment [29], and previously by others [30]. As mentioned previously, this may be of particular importance as ocular muscles are particularly susceptible owing to a relative lack

of complement regulation, reduced safety factor, and simplification of postsynaptic structures.

Without doubt, corticosteroids can be very effective in resolving diplopia, which can be disabling for some patients [31]. However, as part of the natural history of disease, 11–30 % of patients with OMG can achieve spontaneous, long-lasting remission without immunosuppression or pyridostigmine [6, 23, 32]. An early decision to start corticosteroids may expose this group of patients unnecessarily to the risks of corticosteroids, as well as potentially exposing patients to a longer duration of corticosteroids if this were started early, before an adequate trial of symptomatic treatment first. It is our experience that patients who have good control of symptoms on corticosteroids are often reluctant to be completely weaned off corticosteroids for fear of relapse of ocular symptoms. On balance though, the dose of longer-term corticosteroids is likely to be low and therefore with less associated risk of adverse events [33].

It should also be recognized that corticosteroids are not always effective in OMG, whereby 7–33 % of patients have been reported to be non-responders [10, 31]. It is not clear whether this is owing to an inherent difference between non-responders and responders, or whether this is related to the delay in starting corticosteroids. There is a suggestion that both points may hold true. For instance, Kupersmith and Ying [31] have advocated early use of corticosteroids in patients, but, despite this, non-responders still occur. The proportion of never-responders who were started on corticosteroids early (4/55) was similar to the proportion who started corticosteroids late (4/65); as were the proportions of treatment failures for early (7/55) and late (8/65) corticosteroids.

Another aspect that must be considered are the risks associated with corticosteroids. These include avascular bone necrosis, diabetes, hypertension, osteoporosis, opportunistic infection, psychological disturbance, peptic ulcer disease, weight gain, glaucoma, steroid myopathy, and cataract. Our recent study on OMG and SGMG patients showed an adverse event rate of 57 %, despite judicious use of corticosteroids, the breakdown of which is in the following descending order of frequency: 12/47 (25 %) osteoporosis or osteopenia, 8/47 (17 %) diabetes or impaired glycaemic control, 6/47 (13 %) cushingoid appearance, 4/47 (9 %) psychological or sleep disturbance, 3/47 (6 %) infection (one thrush, one encephalitis, one reactivation of old tuberculosis), 2/47 (4 %) gastritis, 2/47 (4 %) cataracts, 2/47 (4 %) central serous retinopathy, 2/47 (4 %) weight gain, 1/47 (2 %) steroid-induced myopathy, 1/47 (2 %) peripheral oedema (Wong et al., submitted). The reported adverse event rate for corticosteroids in MG varies widely (0–67 %) [12, 14–16, 34], but these data were obtained from retrospective studies of variable size ($n=12$ to $n=129$), corticosteroid regimens and duration, proportions of OMG and GMG patients, and methods of monitoring for adverse events. This drawback of previously published work on adverse events on corticosteroids in OMG will be clarified by the EPITOME (Efficacy of Prednisone in the Treatment of Ocular Myasthenia) study [35•].

The EPITOME study is a prospective, multicenter, double blind, randomized, placebo-controlled trial evaluating the efficacy and tolerability of corticosteroids in newly diagnosed OMG patients. The launch of this first well-designed randomized control trial (RCT) of corticosteroids in OMG has been long overdue. This trial was launched in December 2011 and is due to be completed in September 2015 [35•]. Notably, this will be one of the first studies to actively screen for adverse events, including glucose tolerance tests in non-diabetics and glycosylated hemoglobin studies in diabetics at baseline and regular intervals; dual energy X-ray absorptiometry bone density scans at baseline post-treatment time points; and pre- and post-treatment ophthalmological examinations for glaucoma and cataracts [35•].

The EPITOME study aims to recruit 88 patients to examine the efficacy and tolerability of prednisone in early OMG, that is <2 years of disease . The trial runs in two stages of 4-month duration. Prior to entry into stage 1, patients are titrated to the optimum dose of pyridostigmine over a 4-week period. Upon entry into stage 1, patients are randomized to receive either placebo or low-dose prednisone at 10 mg on alternate days. Patients are monitored monthly for safety, tolerability, and efficacy of treatment, and dose is titrated accordingly. At the end of stage 1, patients will enter stage 2 in a double-blinded or open-labeled manner, depending on whether they achieve sustained improvement. Patients who achieve sustained minimal manifestation status according to criteria set by the Myasthenia Gravis Foundation of America [36] will have medication tapered in a double-blinded manner over a 4-month period. Alternatively, patients will be given open-labeled, high-dose prednisone at 60 mg daily if they have not experienced dose-limiting adverse events. The final study visit occurs after 4 months of stage 2. Unfortunately, budgetary constraints mean that other questions of optimal regimen and dosing, and whether the conversion to SGMG will be reduced or merely delayed, will not be addressed by this study. Nevertheless, the results and experience of the EPITOME study will help inform the set up of the next RCTs to answer these questions. The results of the EPITOME study will help clinicians and patients to better weigh the risks and benefits of corticosteroid use.

Another on-going study that will be of interest is the study comparing two tapering strategies of prednisone in myasthenia gravis (MYACOR), due to be completed in Dec 2013. This study compares two tapering strategies of prednisolone in GMG, that is, a rapid strategy (whereby dose is reduced if any improvement reported) versus classical strategy (whereby dose reduced only if minimal manifestation achieved) (Clinicaltrials.gov identifier NCT00987116, accessed 23 June 2013). Patients with OMG are excluded from this trial, but, nonetheless, the information about tapering strategies will be of interest.

Update on Other Forms of Immunosuppression

Despite its drawbacks, corticosteroid therapy is still the recommended first-line immunosuppressant strategy in OMG [2, 37]. To date, no other immunosuppressive drug has been shown to adequately replace corticosteroids as the first-line drug. A recent update in this journal reviewed the other immunosuppressants used in MG [38•]. Unfortunately, many treatment trials of immunosuppresants in MG have been done on patients with GMG only, excluding patients with OMG.

Azathioprine

Azathioprine is the most commonly used and currently recommended [37] adjunct to corticosteroid by acting as a steroid-sparing agent in OMG, and may allow complete weaning of corticosteroids in some patients. It is generally thought to have relatively low teratogenic risk in pregnant women [39]. However, azathioprine has drawbacks, which include a higher risk of cancers, as demonstrated in a recently published case control study of non-thymomatous MG patients [40].

Methotrexate

Methotrexate is currently being investigated as a steroid-sparing agent in MG (clinicaltrials.gov, trial no.NCT00814138, accessed 24 June 2013). This prospective, multicenter, randomized, placebo-controlled trial is due to be completed in December 2013. Unfortunately, patients with OMG are being excluded from this trial. Nevertheless, the outcome will be of interest for patients with OMG. A single-blind trial in newly diagnosed generalized MG of methotrexate versus azathioprine as a steroid-sparing agent was carried out in South Africa. Methotrexate was shown to be an effective, tolerable, and cost-effective alternative to azathioprine [41].

Mycophenolate Mofetil

Mycophenolate mofetil (MMF) has gained favor as a treatment option amongst some MG specialists given promising results from several retrospective studies [42–45], extensive experience with other autoimmune diseases, and ease of its dosing regimen. Two RCTs of MMF have been negative [46, 47]. However, these studies were potentially limited by the use of steroids in the placebo arm that may have masked an effect in the treatment arm, and the duration of follow-up.

Cyclosporine

A randomized, placebo-controlled trial of cyclosporine has shown beneficial effects with regard to muscle strength [48]. A further RCT of prednisone versus prednisone and cyclosporine also demonstrated a beneficial effect on muscle strength with cyclosporine, but without significant steroid-sparing benefit [49]. Of note, its use is limited by its side effect profile, which includes hypertension, neprotoxicity, malignancy, gingival hypertrophy, and hypertrichosis.

Tacrolimus

Another RCT suggests tacrolimus may be effective as a steroid-sparing agent in MG [50]. The secondary analyses of the treatment and control group suggested a steroid-sparing effect of tacrolimus, although the primary end point of the study regarding the dose of prednisolone between the treatment and control group did not reach statistical significance ($P=0.078$). This may have resulted from the study duration being insufficiently long [51]. The authors of this study are therefore currently conducting an extension study on this cohort [50]. Tacrolimus monotherapy has also recently been reported to be effective in a small case series of OMG patients [52]. However, the need for monitoring of drug plasma trough levels, and the potential serious adverse events, for example nephrotoxicity and neurotoxicity from vasculopathies, may limit the use of this drug in OMG [53, 54].

A European working group has been working towards a set of guidelines for the management of OMG, due to be published soon (E. Kerty, personal communication).

Should Patients with OMG have Thymectomy?

Another area of controversy is the use of thymectomy in the treatment of non-thymomatous OMG. There are two aspects to this controversy: if and when thymectomy should be used to treat OMG and, if yes, with which surgical approach.

There seems to be a difference in approach regarding thymectomy according to countries. For example, in the UK and USA, neurologists would generally be reluctant to refer patients for thymectomy unless other treatment options have failed [20]. This contrasts with what some Italian authors have described as their usual practice to offer this option to their patients with OMG [55•].

The controversy is partly contributed by the mixed results of thymectomy in OMG, with some authors describing no benefit to this treatment [10, 56]. Additionally, there are potential risks to surgery. However, with the improvement of techniques, morbidity rates reported range from 4–8 % [55•, 57•, 58•].

Although a number of case series [59, 60] and retrospective studies [57•, 61–66] have suggested benefits to thymectomy in OMG, which include improved symptom control and reduced rate of conversion to GMG, past studies have been criticized for their methodologies, in particular statistical analyses [67]; unclear duration of symptoms before thymectomy; concurrent use of immunosuppression; and small sample size [20]. However, more recently, a number of recent articles have

showed improved rates of remission with early thymectomy in OMG, possibly best within 6 months of symptom onset [55•, 57•, 58•], and in patients with AChR antibodies [58•]. Interestingly, a cost analysis suggests possible advantage of thorascopic thymectomy over medical treatment [68].

The main drawback of all published trials on thymectomy in OMG is the retrospective study design. A number of surgical techniques have been used, including transternal, transcervical, mixed transternal and transcervical, and robotic techniques. The results from different techniques are difficult to compare between different studies and the need for prospective studies to address this question has been emphasized [67].

Currently, there is an on-going prospective thymectomy trial on non-thymomatous MG patients receiving corticosteroids (MGTX), due to be completed in August 2015 (clinicaltrials.gov identifier NCT00294658, accessed 21 June 2013). This multicentre, single-blinded, randomized study aims to compare the degree of symptom control and total prednisone use between patients who have thymectomy in addition to corticosteroid treatment compared with those who do not [69]. Unfortunately, this trial excludes patients with OMG. However, only when the results of these trials are made known will it be appropriate to re-evaluate the role of thymectomy in OMG.

Does Anti-MuSK-positive OMG Exist?

Antibodies to MuSK were first discovered by Hoch et al. [90]. in 70 % of GMG patients who were seronegative for AChR antibodies. MuSK antibodies were subsequently detected in a number of AChR antibody negative MG cohorts (37–48 %) with variation in prevalence that seems to relate partly to geographical location [70–75]. Patients with MuSK antibodies (MuSK–MG) tend to have more severe disease with a predilection for facial, bulbar, and respiratory involvement, and a relatively poor response to therapy, including cholinesterase inhibitors as compared with AChR–MG [70–74]. None of these studies reported OMG patients. Additionally, MuSK antibodies were not found in a cumulative total of 50 seronegative OMG patients from four studies [71–74].

In a study of 110 patients from Italy and the USA, 36 % of patients with MuSK–MG had purely ocular symptoms at onset [76]. All of these patients subsequently developed GMG, usually within 2–3 weeks of symptom onset, though some had ocular symptoms for up to 48 months prior to conversion to GMG. The breakdown of this duration to GMG was not specified in the article. Possible MuSK–OMG has been reported in seven single case reports [77–83]. However, the follow-up duration for three of these cases was no more than approximately 1 year from symptom onset; furthermore, treatment with immunosuppression was given within this period [77–79].

The other four cases provide convincing evidence for the existence of MuSK–OMG [80–83]. These four patients had isolated ocular symptoms without immunosuppression for 2, 2, 3.5, and 12 years, respectively. The two patients with 2 years of purely ocular symptoms were subsequently treated with corticosteroids or azathioprine, without showing evidence of generalization on last review 1 and 2.5 years later, respectively. The patient reported by Chan and Orrison [80] with 12 years of untreated ocular symptoms had extraocular muscle atrophy on magnetic resonance imaging (MRI). The other two cases of normal extraocular MRI with MuSK antibodies were in patients with follow-up of less than 1 year [77, 79].

It is our usual practice to test for both AChR and MuSK antibodies in patients with OMG. From our own recent review of 106 patients with MG under our care, we found one patient with MuSK–OMG who received corticosteroids within 2 years of symptom onset [84].

Serological Developments in Seronegative Patients

In suspected OMG, when faced with clinical uncertainty and reduced single fibre electromyogram sensitivity (by virtue of muscles available for sampling), serological testing is a useful supportive investigation. However, only around half of patients with OMG have antibodies to AChR using the widely available radioimmunoprecipiation assay. This assay detects the presence of antibody binding to radioactively-labeled AChRs in solution. Consequently, the receptors are not clustered, as they are in vivo. Cell-based assays have now been developed to detect antibodies on the surface of cells expressing AChR or MuSK in their native conformation, and clustered as they are in vivo [85]. Up to 50 % of seronegative OMG sera, from the Oxford archives, have been shown to have clustered AChR antibodies, predominantly of the IgG1 subclass that are capable of activating complement [86•]. However, it must be appreciated that these were patients studied over a number of years and may not be representative of the patients seen at onset of disease in other, less-specialized centers.

Recently, a variable number of patients have been shown to have antibodies against the LRP4 (2–50 %) [87•, 88, 89]. LRP4 forms a complex with MuSK and, in keeping with this, the phenotype thus far appears to resemble that of MuSK–MG.

As these antibody techniques are refined and applied to other seronegative cohorts the prevalence and phenotypes will become clearer, and this may help to provide a serological diagnosis in “seronegative” cases.

Conclusions

The management of OMG can be difficult and varies between centers. We have highlighted a number of areas of controversy

in this regard. The rarity of OMG and lack of RCTs contributes to this controversy. However, it is not impossible to address this, as demonstrated by a number of currently on-going RCTs, for example the EPITOME and the thymectomy studies mentioned above. Finally, in the next few years the completion of a number of on-going clinical trials on GMG will help inform our management and provide lessons for future trials in the management of OMG. An important decision for the future will be whether the conclusions of trials involving GMG can be extrapolated to OMG.

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Compliance with Ethics Guidelines

Conflict of Interest Sui H. Wong and Gordon T. Plant declare that they have no conflict of interest. Angela Vincent and the University of Oxford hold patents and receive royalties and payments for autoantibody tests including MuSK antibodies.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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