Mycophenolate plus methylprednisolone versus methylprednisolone alone in active, moderate-to-severe Graves' orbitopathy (MINGO): a randomised, observer-masked, multicentre trial

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Summary

Background European guidelines recommend intravenous methylprednisolone as first-line treatment for active and severe Graves' orbitopathy; however, it is common for patients to have no response or have relapse after discontinuation of treatment. We aimed to compare the efficacy and safety of add-on mycophenolate to methylprednisolone in comparison with methylprednisolone alone in patients with moderate-to-severe Graves' orbitopathy.

Methods MINGO was an observer-masked, multicentre, block-randomised, centre-stratified trial done in two centres in Germany and two in Italy. Patients with active moderate-to-severe Graves' orbitopathy were randomly assigned to receive intravenous methylprednisolone (500 mg once per week for 6 weeks followed by 250 mg per week for 6 weeks) either alone or with mycophenolate (one 360 mg tablet twice per day for 24 weeks). The prespecified primary endpoints were rate of response (reduction of at least two parameters of a composite ophthalmic index [eyelid swelling, clinical activity score, proptosis, lid width, diplopia, and eye muscle motility] without deterioration in any other parameter) at 12 weeks and rate of relapse (a worsening of symptoms that occurred after a response) at 24 and 36 weeks. Rates of response at week 24 and sustained response at week 36 were added as post-hoc outcomes. Prespecified primary outcomes and post-hoc outcomes were assessed in the modified intention-to-treat population (defined as all patients assigned to treatment who received at least one infusion of methylprednisolone, when outcome data were available), and safety was assessed in all patients who received at least one dose of study drug. This trial is registered with the EU Clinical Trials Register, EUDRACT number 2008-002123-93.

Findings 164 patients were enrolled and randomised between Nov 29, 2009, and July 31, 2015. 81 were randomly assigned to receive methylprednisolone alone and 83 to receive methylprednisolone with mycophenolate. In the intention-to-treat population at 12 weeks, responses were observed in 36 (49%) of 73 patients in the monotherapy group and 48 (63%) of 76 patients in the combination group, giving an odds ratio (OR) of 1·76 (95% CI 0·92–3·39, p=0·089). At week 24, 38 (53%) of 72 patients remaining in the monotherapy group and 53 (71%) of 75 patients remaining in the combination therapy group had responded to treatment (2·16, 1·09–4·25, p=0·026). At week 24, relapse occurred in four (11%) of 38 patients in the monotherapy group and four (8%) of 53 patients in the combination group (OR 0·71, 0·17–3·03, p=0·72). At week 36, relapse occurred in an additional three (8%) patients in the monotherapy group and two (4%) patients in the combination group (0·65, 0·12–3·44, p=0·61). At week 36, 31 (46%) of 68 patients in the monotherapy group and 49 (67%) of 73 patients in the combination group had a sustained response (OR 2·44, 1·23–4·82, p=0·011). 23 patients had 24 serious adverse events, with 11 events in ten patients in the combination group and 13 events in 13 patients in the monotherapy group. Mild and moderate (grade 1–2) drug-related adverse events occurred in 16 (20%) of 81 patients receiving monotherapy and 21 (25%) of 83 patients receiving combination therapy (p=0·48).

Interpretation Although no significant difference was seen in the rate of response at 12 weeks or rate of relapse at 24 and 36 weeks, post-hoc analysis suggested that addition of mycophenolate to treatment with methylprednisolone improved rate of response to therapy by 24 weeks in patients with active and moderate-to-severe Graves' orbitopathy.

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Introduction

Graves' orbitopathy is an autoimmune disorder that is associated with poor clinical outcomes, including impaired quality of life and socioeconomic status.[1] Several clinical variants of Graves' orbitopathy exist, including euthyroid Graves' orbitopathy, which has been listed as a rare disease in Europe.[2] The Guidelines of the European Thyroid Association and the European Group on Graves' Orbitopathy (EUGOGO) recommend intravenous methylprednisolone as first-line treatment

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Research in context

Evidence before this study

Before beginning the study, we searched PubMed for reports of randomised, double-blind, or observer-masked trials in patients with Graves' orbitopathy published in any language up to autumn, 2008, using the search terms "Graves' orbitopathy", "thyroid-associated orbitopathy", "thyroid eye disease", "management", "immune suppressive treatment", "intravenous steroids", and "non-steroidal immunosuppressants". We excluded uncontrolled studies and case reports. Other than the administration of high-dose pulses of intravenous steroids and eventually the combination of orbital irradiation with oral steroid therapy, no randomised, double-masked or single-masked trials had convincingly demonstrated alternative treatment approaches in this research field. The 2016 European Thyroid Association guidelines recommend intravenous methylprednisolone pulse therapy as first-line treatment for active and severe Graves' orbitopathy. However, some patients do not respond or relapse after completion of steroid treatment. There is therefore a need to identify new therapeutic strategies, including combination therapies.

Added value of this study

To our knowledge, this study is the first to investigate the efficacy and safety of add-on mycophenolate to methylprednisolone for moderate-to-severe Graves' orbitopathy. Although our prespecified primary analyses did not show significant differences between groups, post-hoc analyses suggest that the addition of mycophenolate sodium, a lymphocyte proliferation-inhibiting drug, to the current first-line anti-inflammatory and immunosuppressive treatment for this complex autoimmune orbital disease significantly enhances the efficacy of the intravenous steroid therapy after 24 weeks, without increasing the frequency of treatment-associated adverse effects. Therefore, in patients with active and severe Graves' orbitopathy and no contraindications for mycophenolate sodium, combination therapy with this drug could be considered.

Implications of all the available evidence

To significantly improve or optimise the response rate of immunosuppressive, anti-inflammatory first-line treatment for patients with active and severe Graves' orbitopathy, the available evidence supports the use of a combination treatment of drugs involved at different phases in the immunopathogenesis of this disorder. Future research will need to focus on the relevance of potential crosstalk between the thyroid stimulating hormone (TSH) receptor, a classic autoantigen in autoimmune thyroid disease, and other recently introduced potential co-autoantigens, such as the insulin-like growth factor-1 receptor, as well as their targeting through recently introduced TSH receptor monoclonal autoantibodies or TSH receptor-binding small peptides.

for active and severe Graves' orbitopathy,[3] and weekly administration of methylprednisolone for 12 weeks has become standard practice in the management of Graves' orbitopathy.[3,4] Methylprednisolone inhibits prostaglandin secretion, fibroblast activity, and glycosaminoglycan production.[5] Additionally, high-dose methylprednisolone reduces the number of circulating dendritic cells[6] and decreases serum concentrations of thyroid-stimulating hormone receptor autoantibodies (TSHR-Ab).[7] Methylprednisolone monotherapy leads to satisfactory outcomes in most patients with active, moderate-to-severe Graves' orbitopathy; however, some patients do not respond or have relapse after completing treatment, and progression to dysthyroid optic neuropathy in non-responders does not seem to be prevented by this approach.[8] Although higher cumulative doses of methylprednisolone are associated with slightly improved response rates, the frequency of serious adverse events rises to unacceptable levels.[3,5] There is therefore a need to identify new therapeutic strategies, of which combined therapies are worth exploring.

Mycophenolate mofetil inhibits inosine monophosphate dehydrogenase, leading to inhibition of the de-novo pathway for guanosine monophosphate synthesis.[9] Mycophenolate mofetil also inhibits the proliferative responses of T and B lymphocytes to both mitogenic and allospecific stimulation, and suppresses antibody formation by B lymphocytes.[10] Furthermore, mycophenolate mofetil decreases expression of adhesion molecules via guanosine triphosphate depletion, thus potentially modulating the chemotaxis of infiltrating activated lymphocytes in inflammatory tissue.[11] In patients with lupus erythematosus, mycophenolate mofetil is recommended as second-line treatment.[12] Because most side-effects of mycophenolate mofetil are gastrointestinal, film-coated, gastro-resistant tablets containing the active substance as a sodium salt were developed and maintenance therapy can be safely switched from mycophenolate mofetil to the enteric-coated mycophenolate sodium (mycophenolate).[13,14]

On the basis of the antiproliferative mechanism of mycophenolate, we postulated that it would have a beneficial effect in Graves' orbitopathy, and aimed to study the efficacy and tolerability of combined therapy with methylprednisolone and mycophenolate compared with methylprednisolone monotherapy in active, moderate-to-severe Graves' orbitopathy. The rationale for the addition of a non-steroidal immunosuppressive agent to methylprednisolone was to combine anti-proliferative and anti-inflammatory effects.

Methods

Study design and participants

The randomised, observer-masked, multicentre, open-label mycophenolate sodium in Graves' orbitopathy (MINGO) trial was based at four EUGOGO academic

tertiary orbital centres with joint thyroid eye clinics, of which two were in Germany and two in Italy, and to which patients were referred from across the respective countries. The trial was approved by all local ethical committees and written consent was obtained from all patients. The study protocol is available in the appendix.

Patients aged 18–75 years were eligible to participate if they had euthyroidism for at least 2 months with antithyroid drugs or after thyroidectomy, or 6 months after radioiodine administration; had active, thyroid eye disease (clinical activity score of 3–7)[1,3] that was moderate to severe (moderate-to-severe active soft tissue involvement [according to the EUGOGO colour atlas evaluation], proptosis ≥22 mm, eye muscle involvement with mono-ocular ductions in any direction of gaze of less than 30° or evident dysmotility, or diplopia [Gorman score of grade 1–3]). To be eligible, patients could not have received previous immunosuppressive treatment for Graves' orbitopathy, or received corticosteroids or other immunosuppressive agents within the past 3 months for any reason. Patients with optic neuropathy, acute or chronic viral hepatitis, any relevant malignancy, or chronic renal failure were excluded. A complete list of inclusion and exclusion criteria is available in the appendix (p 1).

Randomisation and masking

Patients who fulfilled the inclusion criteria in the absence of exclusion criteria were centrally registered and randomised. The randomisation schedule was generated by an independent statistician before study activation and was stratified by site in blocks of sixteen. All patients were assigned to one of two treatment groups (methylprednisolone or methylprednisolone plus mycophenolate) in a 1:1 ratio. The randomly assigned treatment was then communicated via fax to the investigator in each orbital centre. All ophthalmologists and the Johannes Gutenberg University expert statistician were masked to group assignment. Although the thyroid investigators were aware of the medication received, they emphasised that ophthalmologists should not enquire about the medication received and that patients should not inform the observer ophthalmologists regarding their current treatment.

Procedures

During the first 12 weeks, intravenous methylprednisolone was administered to all patients at 500 mg once per week for 6 weeks, then 250 mg once per week for 6 weeks with a cumulative dose of 4·5 g.[7] Patients in the monotherapy group received this intravenous methylprednisolone only. In addition to the methylprednisolone, patients in the combination methylprednisolone and mycophenolate group also received 360 mg of mycophenolate orally twice per day for 24 weeks with a cumulative mycophenolate dose of 120 g (figure 1), a commonly used dose in patients with autoimmune diseases.[12]

All patients underwent complete ophthalmic and endocrine assessment at baseline and 6, 12, 24, and 36 weeks after starting treatment. The clinical activity and severity (judged on the NOSPECS scale) of Graves' orbitopathy were assessed in accordance with the EUGOGO recommendations.[3,15] Ophthalmic assessment was done by an ophthalmologist masked to the treatment received, using the EUGOGO case record form[4,15] including the items soft tissue involvement (inflammatory eyelid swelling), lid width in mm, clinical severity score, clinical activity score (seven items), proptosis in mm measured with the Hertel exophthalmometer, eye muscle motility assessed with orthoptic measurements of mono-ocular ductions (in degrees) in four directions of gaze (perimeter arc), the Gorman diplopia score, and visual acuity using the Snellen chart in decimals. Graves' orbitopathy was classified as active if at least three of the following seven features were present: orbital pain at rest, gaze-provoked orbital pain, lid swelling, lid redness, conjunctiva redness, chemosis, or swelling of the caruncle. Diplopia was scored as none (0 points), intermittent (1 point), inconstant (at certain gaze directions only, 2 points), or constant (in primary position, 3 points). Lid fissure was measured with a ruler in the primary gaze position.

All patients filled out the EUGOGO quality of life questionnaire at baseline and weeks 12, 24, and 36. This questionnaire consists of two subscales: one for visual function (eight questions referring to limitations attributable to decreased visual acuity, diplopia, or both) and one for appearance (eight questions referring to limitations in psychosocial functioning attributable to changes in appearance). The questions are scored as severely limited (1 point), a little limited (2 points), or not

See Online for appendix

For the **EUGOGO colour atlas** see www.eugogo.eu

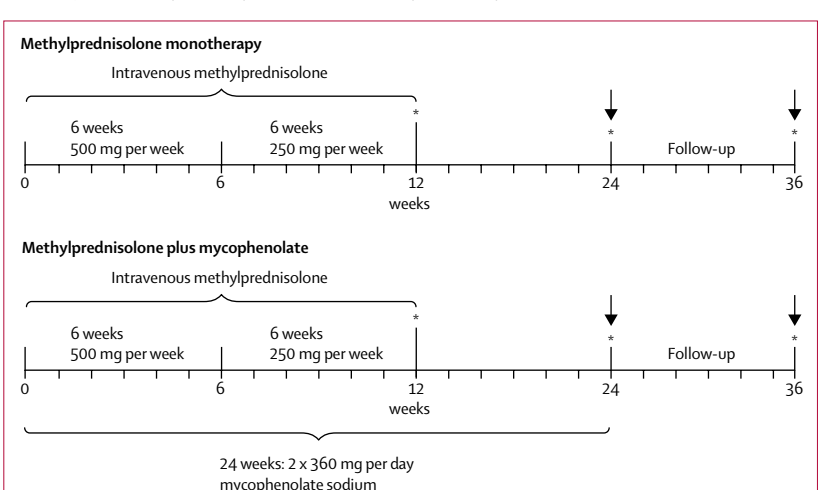

Figure 1: **Study design**
The labels indicate the timepoints for the outcomes. Prespecified outcomes are represented by * and post-hoc outcomes are represented by an arrow. Endocrine and ophthalmic investigations were done at baseline and 6, 12, 24, and 36 weeks after starting therapy. Safety parameters were assessed at weeks 6, 12, and 24.

limited at all (3 points). The two raw scores (8–24 points) can be transformed to total scores (zero to 100) using the formula:

$$total\ score = 100\left(\frac{raw\ score - x}{2x}\right)$$

where x stands for the number of completed questions. For both scores, higher scores indicate better quality of life. Improvement or deterioration in quality of life was defined as an increase or decrease of 6 points or more in total score on either of the two quality of life scales, respectively. No change was defined as change of fewer than 6 points in either direction.[16]

Outcomes

In the original study protocol, the prespecified primary outcomes were response rate at week 12 and relapse rates at weeks 24 and 36. We also decided to examine the response at week 24 as a post-hoc outcome to represent the response to therapy in both groups at the end of treatment. Figure 1 shows the timepoints for the various primary (prespecified) and post-hoc outcomes.

The prespecified definition of response was improvement in the most affected eye, defined as a reduction of at least two measures of a composite index without simultaneous deterioration of any of the ophthalmic parameters of the index. Prespecified improvement of Graves' orbitopathy was defined as reduction of at least two measures in the composite index in at least one eye, without deterioration in any of the same measures in either eye. The composite index measures were improvement of eyelid swelling in accordance with the EUGOGO colour atlas, improvement in clinical activity score of at least 2 points, improvement in proptosis of at least 2 mm, improvement in lid width of at least 2 mm, improvement in diplopia (disappearance or change in the degree), and improvement of at least 8° in eye muscle motility. Prespecified deterioration of Graves' orbitopathy (recurrence or relapse relative to baseline) was defined as change in two of the following outcome measures in at least one eye: worsening of inflammatory eyelid swelling, worsening of clinical activity score of at least 2 points, worsening of proptosis of more than 2 mm, worsening of lid width of at least 2 mm, worsening of diplopia, deterioration of eye muscle motility, and occurrence of dysthyroid optic neuropathy. Prespecified lack of change in orbitopathy was defined as an absence of changes or changes smaller than those defined in any of the previously mentioned parameters. Overall response to immunosuppressive treatment in both study groups was defined post-hoc as improvement of ophthalmic symptoms and signs at weeks 24 and 36 compared with baseline, without any deterioration of any ophthalmic findings.

Adverse events were documented and coded in accordance with the standardised medical dictionary for regulatory affairs (MedDRA),[17–19] as recommended by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH).[20] Adverse events were assessed for any alternative cause while judging relatedness to intake of mycophenolate (ie, events deemed side-effects if related). Adverse events were followed up until a stable outcome could be documented or until the patient was lost to follow-up. Seriousness of adverse events was established with the seriousness criteria defined in the ICH E6 guideline for clinical practice.[21] Patients exiting the study because of adverse events or side-effects or worsening of Graves' orbitopathy were kept in the primary analysis. White blood cell counts, liver enzymes, serum thyroid-related hormones, and TSHR-Ab (by electrochemiluminescent immunoassay [CLIA, Abbott, Wiesbaden, Germany] with a cutoff of 1·8 IU/L) were measured at weeks 0, 6, 12, 24, and 36.

Statistical analysis

For the primary outcome, we estimated that a sample size of 75 patients per group would have 80% power to detect a difference in response rates between 85% (methylprednisolone plus mycophenolate) and 65% (methylprednisolone) with a type I error of 0·05 and a two-sided χ^2 test of trend in proportions based on a logistic model. Statistical analysis was done with SPSS (version 22.0). We characterised the distribution of metric variables by reporting median and quartiles or means and standard deviation when appropriate. For dichotomous variables, we show absolute and relative frequencies. All outcomes were adjusted for multiple comparisons. For the prespecified primary outcomes and the post-hoc outcomes, we compared the proportions of patients having response or relapse using Fisher's exact test and reported the treatment effect as an odds ratio (OR) with 95% CIs. As a post-hoc analysis, we classified the patients evaluable at week 36 into three ordered categories according to response at week 24 and sustained response at week 36, and compared treatment groups with respect to this ordinal classification using the Mantel Haenszel χ^2 test for trend. To assess possible attrition bias, we did a post-hoc sensitivity analysis fitting a logistic model for longitudinal binary data to the outcome response at week 12 and week 24 and sustained response at week 36 using the method of generalised estimation equations. Treatment effects at all timepoints are reported as ORs and 95% CIs. We did post-hoc subgroup analyses of treatment effects with respect to response at week 24 by testing for interaction in a logistic model and we report these non-selectively. Subgroup specific treatment ORs and 95% CIs are presented as a forest plot. We did further post-hoc comparisons between treatment groups with respect to single variables contributing to the primary composite outcome using the Mann-Whitney U test for continuous variables and the χ^2 test or Fisher's exact test for dichotomous variables.

We report p values for findings at week 24 only to limit the number of tests and avoid inflation of type I error. All reported p values are two-sided and the significance level was set at 0·05. We analysed prespecified primary outcomes, post-hoc outcomes, and secondary outcomes in the modified intention-to-treat population, which included all patients assigned to treatment who received at least one infusion of methylprednisolone, when outcome data were available. We assessed safety in all patients who received at least one dose of study drug.

This trial is registered with the EU Clinical Trials Register, EUDRACT number 2008-002123-93.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

197 patients with active and moderately severe Graves' orbitopathy were eligible to participate in the study; however, 33 had thyroid dysfunction or declined to receive mycophenolate. 164 patients with clinically active moderate-to-severe Graves' orbitopathy were enrolled at four EUGOGO academic centres (116 in Mainz, 21 in Essen, 16 in Milan, and 11 in Pisa). All patients underwent randomisation between Nov 29, 2009, and July 31, 2015. Of the 164 patients entering randomisation, 81 were assigned to methylprednisolone monotherapy and 83 to methylprednisolone plus mycophenolate. Demographic and clinical data are shown in table 1. There were no relevant differences at baseline between the study groups with respect to sex, age, duration of Graves' orbitopathy, proportion of smokers, thyroid treatment, ophthalmic clinical activity score, severity of Graves' orbitopathy, and serum concentrations of thyroid stimulating hormone and TSHR-Ab.

Of the 164 patients enrolled, ten were excluded before receiving medication (figure 2), leaving 75 patients in the methylprednisolone group and 79 in the methylprednisolone plus mycophenolate group. Of the 154 patients who received any treatment, 150 completed assessments and treatments at week 6, 149 at week 12, 147 at week 24, and 141 at week 36 (figure 2). During the treatment period, dysthyroid optic neuropathy was registered early in four patients in the monotherapy group between weeks 4 and 12, whereas dysthyroid optic neuropathy occurred after week 16 in five patients in the combination group. The nine dysthyroid optic neuropathy cases were regarded as treatment failure. In the 12 week follow-up period, two additional cases of dysthyroid optic neuropathy occurred in patients in the combination group who previously had responses and were deemed to represent a relapse.

	Methylprednisolone (n=81)	Methylprednisolone plus mycophenolate (n=83)
Demographics		
Age (years)	50·6 (10·0)	52·1 (10·1)
Height (m)	1·686 (0·085)	1·679 (0·089)
Bodyweight (kg)	73·6 (17·9)	72·6 (14·8)
Systolic blood pressure (mm Hg)	123·6 (13·8)	128·1 (17·2)
Diastolic blood pressure (mm Hg)	79·8 (8·7)	82·3 (10·9)
Female	64 (79%)	61 (73%)
Menopause (women only)	41 (64%)	42 (69%)
Concomitant diseases	1·9 (1·6)	2·1 (1·8)
Concomitant medications	2·5 (1·9)	1·9 (1·9)
Smoking status		
Smoker	41 (51%)	44 (53%)
Pack years	16 (7–30)	19 (11·5–26·25)
Cigarettes per day	5 (0–10)	6·5 (0–14·75)
Never smoked	22 (27%)	16 (19%)
Clinical characteristics		
Duration of thyroid disease (months)	15 (5–48)	13·5 (6·25–42)
Graves' disease	75 (93%)	78 (94%)
Hashimoto's thyroiditis	2 (2%)	4 (5%)
No clinical or biochemical thyroid disease (euthyroid orbitopathy)	4 (5%)	1 (1%)
Visible goitre	7 (9%)	5 (6%)
Duration of antithyroid drugs (months)	6 (3–16)	5·5 (2·25–15)
Antithyroid drugs	33 (41%)	34 (41%)
Previous antithyroid medication	44 (54%)	44 (53%)
Relapse of hyperthyroidism	11 (14%)	14 (17%)
Levothyroxine substitution	34 (42%)	35 (42%)
No thyroid drugs	11 (14%)	12 (14%)
Radioiodine therapy	16 (20%)	15 (18%)
Thyroidectomy	18 (22%)	24 (29%)
Dermopathy	1 (1%)	0
Orbital disease		
Duration of orbital disease (months)	8·5 (4–18)	9 (5–19·5)
Diplopia	52 (64%)	55 (66%)
Diplopia in all gazes	9 (11%)	13 (16%)
Abnormal head posture	9 (11%)	11 (13%)
Binocular vision without prism	57 (70%)	60 (72%)
Orthothropia	58 (72%)	59 (71%)
Blurred vision	45 (56%)	51 (61%)
Photophobia	61 (75%)	71 (86%)
Excessive watering	59 (73%)	69 (83%)
Grittiness	56 (69%)	57 (69%)
Serology		
Thyroid stimulating hormone autoantibody (cutoff <1·8 IU/L)	8·9 (2·35–18·2)	7·2 (2·35–14·1)
Thyroid stimulating hormone (normal range 0·4–4·9 mU/L)	0·52 (0·42–0·95)	0·72 (0·49–1·83)

Data are median (IQR), mean (SD), or n (%).

Table 1: **Demographic and clinical data by study groups**

At week 12, 36 (49%) of 73 patients responded in the methylprednisolone group and 48 (63%) of 76 patients responded in the methylprednisolone plus mycopheno-

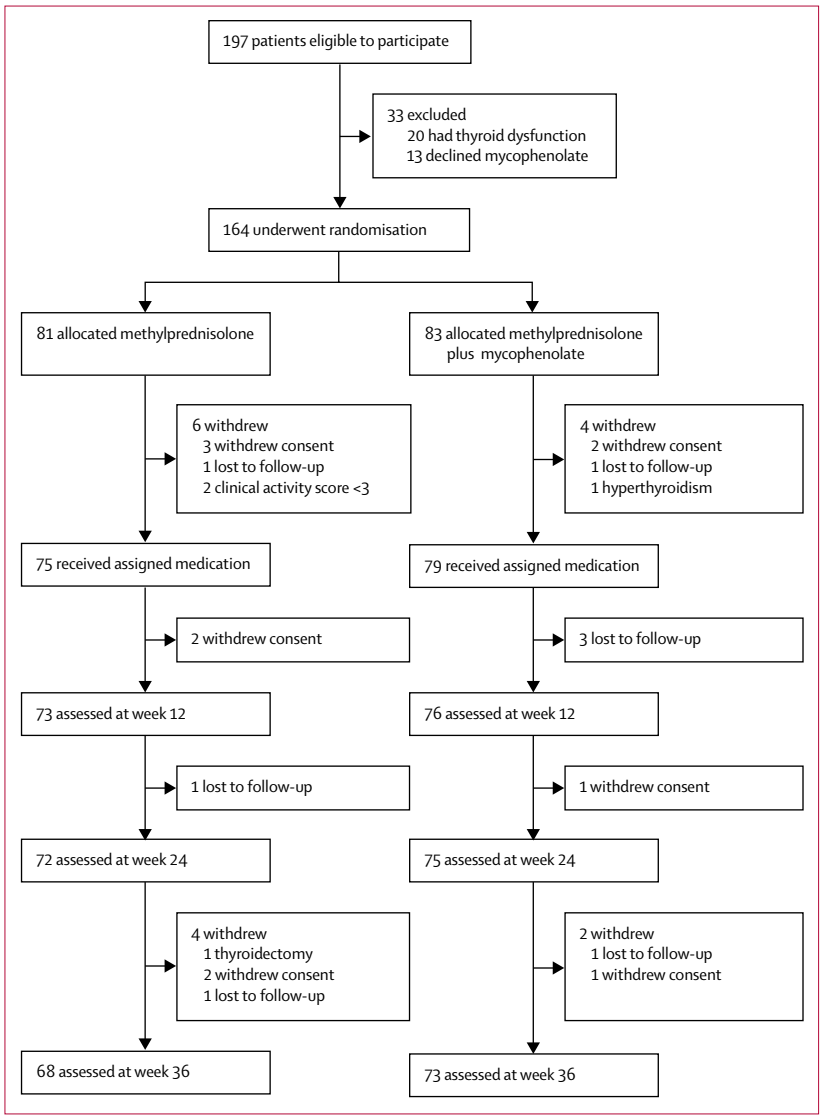

Figure 2: **Trial profile**

late group (OR 1·76, 95% CI 0·92–3·39, p=0·089). Relapses occurred in four (11%) of 38 patients in the monotherapy group and four (8%) of 53 patients in the combination group at week 24 (OR 0·71, 0·17–3·03, p=0·72). At week 36, further relapses occurred in three (8%) patients in the monotherapy group and two (4%) patients in the combination group (OR 0·65, 0·12–3·44, p=0·61).

201 adverse events occurred in 79 (48%) of 164 patients, without any suspected unexpected serious adverse events. The most common adverse events were eye surgery (12 [7%] patients) and insomnia (11 [7%] patients). 24 serious adverse events, including thyroidectomy, orbital decompression surgery for dysthyrod optic neuropathy, and inpatient treatment due to unspecific general symptoms, occurred in 23 (14%) patients, including 11 events in ten patients in the methylprednisolone group and 13 in the methylprednisolone plus mycophenolate group. 68 drug-related side-effects were noted in 37 (23%) patients. Side-effects occurred in 16 (20%) of 81 patients in the monotherapy group and in 21 (25%) of 83 patients in the combination group (p=0·48). Overall, 29 (19 grade 1 and ten grade 2) side-effects were reported in the monotherapy group and 39 (31 grade 1 and eight grade 2) were reported in the combination therapy group (table 2). No patients needed dose reductions or discontinued the trial because of drug-related toxic effects.

In the post-hoc analysis at week 24, responses were achieved by 38 (53%) of 72 patients in the methylprednisolone group and 53 (71%) of 75 patients in the methylprednisolone plus mycophenolate group (OR 2·16, 95% CI 1·09–4·25, p=0·026). At the week 36 post-hoc analysis, 31 (46%) of 68 in the monotherapy group and 49 (67%) of 73 patients in the combination group had a sustained response (OR 2·44, 1·23–4·82, p=0·011).

We compared the outcomes for the monotherapy and combination groups in a post-hoc longitudinal data analysis model that takes into account the correlation within individuals using longitudinal data for outcomes at weeks 12, 24, and 36 (responses at weeks 12 and 24 and sustained response at week 36). This model produced ORs of 1·76 (95% CI 0·92–3·39, p=0·090) for week 12 responses, 2·14 (1·09–4·20, p=0·027) for week 24 responses, and 2·23 (1·14–4·35; p=0·019) for sustained responses at week 36.

In a post-hoc subgroup analysis (figure 3) of week 24 treatment effect of monotherapy versus combination therapy, we did not find significant differences between the treatment groups when considering the variables smoking history, duration of Graves' orbitopathy, clinical activity of Graves' orbitopathy, serum concentration of TSHR-Ab, and sex. Overall, the proportion of patients with worsening of orbitopathy at weeks 12, 24, and 36 was similar between groups. During the 12 week follow-up period (weeks 24–36), nine (13%) of 72 patients in the monotherapy group and 13 (17%) of 75 patients in the combination group had further responses (OR 1·47, 0·59–3·68).

Overall, ophthalmic improvement was noted at weeks 12, 24, and 36 in both study groups (figure 4). Post-hoc analysis showed that results in the methylprednisolone plus mycophenolate group were significantly better than those in the methylprednisolone group at weeks 24 and 36, with more patients having improvements in the methylprednisolone plus mycophenolate group. Clinical activity score in the left eye (the study eye for most patients) decreased significantly more in the combination treatment group at week 12 than in the monotherapy group (table 3). Similarly, the number of patients with swelling of the left eyelids or caruncle decreased significantly more in the combined treatment group (table 3; appendix pp 2–4). Significant improvements in downgaze duction and ocular adduction occurred

	Methylprednisolone	Methylprednisolone plus mycophenolate
Total	29	39
Cardiac disorders	0	1
Palpitations	0	1
Ear and labyrinth disorders	1	1
Vertigo	1	1
Gastrointestinal disorders	5	10
Abdominal discomfort	2	5
Nausea	1	2
Dyspepsia	1	2
Gastritis	1	0
Diarrhoea	0	1*
General disorders and administration site reactions	2	4
Fatigue	2	2
Feeling cold or hot	0	2
Infections and infestations	5	5
Cystitis	2*	2*
Oral fungal infection	2*	0
Herpes simplex	0	1*
Herpes zoster	0	1*
Sinusitis	0	1*
Bronchitis	1	0
Injury, poisoning, and procedural complications	0	1
Scratch	0	1
Investigations	1	3
Increase in serum liver enzyme concentrations	1	2
Weight increase	0	1
Metabolism and nutrition disorders	2	2
Hyperglycaemia	2*	1*
Decreased appetite	0	1
Musculoskeletal and connective tissue disorders	0	2
Myalgia	0	2
Nervous system disorders	2	2
Headache	2	1
Dizziness	0	1
Psychiatric disorders	3	4
Sleeping disorders	2	3
Depressive mood	1*	1*
Reproductive system and breast disorders	1	0
Metrorrhagia	1*	0
Skin and subcutaneous tissue disorders	2	2
Psoriasis	1	0
Eczema	0	1
Hyperhidrosis	0	1
Rash	1	0
Vascular disorders	5	2
Hot flush	2	1
Face swelling (mild)	1	1
Hypertension	2*	0

(Table 2 continues in next column)

(Table continued from previous column)

Treatment-related adverse effects were recorded and coded according to the standardised MedDRA and System Organ Class as recommended by the ICH. All adverse events were analysed for any alternative cause while judging relatedness to intake of study drugs. The seriousness of treatment-related adverse effects was established according to seriousness criteria defined in the ICH E6 guideline for Clinical Practice. MedDRA=Medical Dictionary for Regulatory Affairs. ICH=International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. *Moderate, not mild, severity.

Table 2: **Study drug-related side-effects**

only in the combination group, with significant differences between the two treatment groups for downgaze duction and elevation (table 3). Additionally, significant improvements in the visual function scale were noted only in the combination group (appendix pp 2–4). Similar findings were also seen for the number of patients with orbital pain as an individual inflammatory symptom (appendix pp 2–4) or chemosis as a classic inflammatory sign, which declined more in the combination group than in the methylprednisolone group (appendix).

In both study groups, significant improvements were reported in the total quality of life score, the quality of life appearance and visual function scales, clinical activity and clinical severity (NOSPECS) scores, proportion of patients with conjunctiva injection or eyelid erythema, and serum concentrations of TSHR-Ab (appendix pp 2–4). No significant differences were detected between the study groups for these measures.

Over 36 weeks, 90 of 147 (61%) patients responded to monotherapy or combination therapy (appendix pp 5, 6). In another post-hoc analysis, we compared baseline values between patients who had a response and those who did not. We detected significant differences between responders and non-responders in the baseline values for quality of life, duration of Graves' orbitopathy, proportion of patients with blurred vision, and serum concentrations of TSHR-Ab (appendix p 5).

Discussion

In this randomised, observer-masked, multicentre trial, the prespecified primary outcomes were negative, showing no statistically significant differences between

the two treatment groups by week 12. However, the results of post-hoc analyses suggest that there is an advantage to the addition of mycophenolate, a lymphocyte proliferation-inhibiting agent, to an established 12-week course of intravenous methylprednisolone treatment in patients with active moderate-to-severe Graves' orbitopathy. Although the duration of immunosuppressive therapy (12 weeks of methylprednisolone *vs* 24 weeks of mycophenolate) might have affected the results, the response rate was significantly higher in the methylprednisolone plus mycophenolate group at the post-hoc timepoint of 24 weeks, without an increased frequency of drug-induced adverse events. The relapse rate was low during the follow-up observation period, and the number of patients with an overall improvement in their ophthalmic parameters was higher at weeks 24 and 36 in the methylprednisolone plus mycophenolate group than in the methylprednisolone group. The EUGOGO disease-specific questionnaire showed a significant increase of patients' quality of life both during and after immunosuppressive treatment. This finding suggests that, as seen in patients with active severe Graves' orbitopathy,[22] the effect of intravenous methylprednisolone might continue after the completion of therapy.

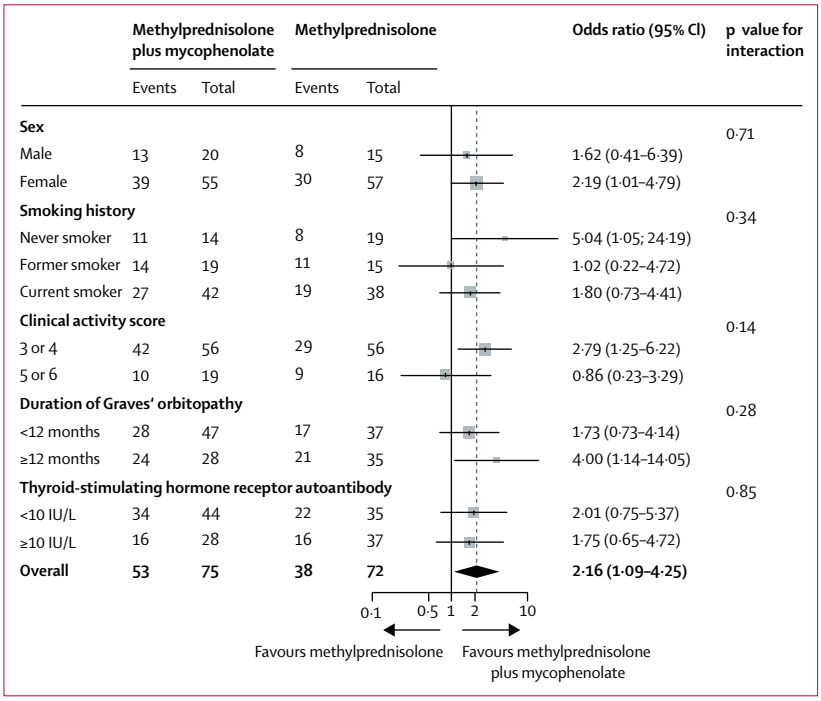

Figure 3: **Post-hoc subgroup analysis of treatment response at 24 weeks**
The dashed vertical line shows the overall treatment effect of methylprednisolone plus mycophenolate compared with methylprednisolone alone. For each subgroup, the square is proportional to the number of patients and represents the point estimate of the treatment effect and the horizontal lines represent the 95% CIs.

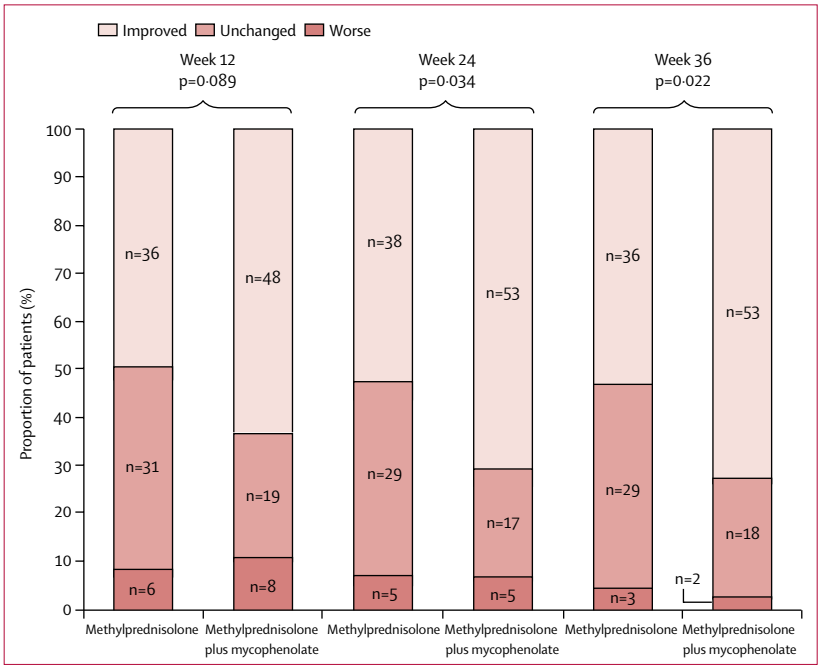

Figure 4: **Post-hoc analysis of treatment effect on Graves' orbitopathy compared with baseline**
Compared with baseline, percentage of patients with either overall ophthalmic improvement, no change, or worsening disease. p values were calculated with Fisher's exact test as a post-hoc analysis.

We can compare the efficacy of treatment in our study to that in the previous EUGOGO intravenous methylprednisolone dose trial.[8] Our results support the inactivation of Graves' orbitopathy, with 80% of the study patients having inactive eye disease at week 24 with a clinical activity score less than 3, while only a mild improvement of eye muscle duction was noted. In the methylprednisolone dose comparison trial,[8] higher single or cumulative methylprednisolone doses (ie, 750 mg per pulse or 7·5 g as a total dose) seemed to have greater effects on ocular duction and diplopia. In our study, the intermediate cumulative methylprednisolone dose of 4·5 g did not entirely prevent the occurrence of dysthyroid optic neuropathy. However, the relapse rate was lower in our trial than in the previous EUGOGO study, and our 4·5 g intravenous methylprednisolone dose was well tolerated overall; no major treatment-related adverse effects were recorded and no premature dropouts occurred due to serious adverse events. In line with this safety finding, and in contrast with the EUGOGO trial, quality of life improved steadily in both treatment groups in our study.

The safety analysis showed acceptable drug tolerability for both methylprednisolone and mycophenolate. To prevent the previously described gastrointestinal adverse effects that occur with mycophenolate mofetil,[23] we used a mycophenolate compound that is reported to have improved gastrointestinal tolerability.[14] No serious adverse events occurred during our trial, and no patient had to stop treatment because of treatment-related adverse effects. By contrast, in patients undergoing kidney transplant who received mycophenolate mofetil, dropout rates due to adverse events varied between 10% and 25%.[23,24] Our results support the conclusions of the mycophenolate mofetil study,[24] a large European multi-

	Outcome by treatment group								Adjusted mean between-group difference (95% CI), p value		
	0 weeks		12 weeks		24 weeks		36 weeks		12 weeks	24 weeks	36 weeks
	Methylpred-nisolone	Methylpred-nisolone plus mycophenolate	Methylpred-nisolone	Methylpred-nisolone plus mycophenolate	Methylpred-nisolone	Methylpred-nisolone plus mycophenolate	Methylpred-nisolone	Methylpred-nisolone plus mycophenolate			
Quality of life score											
Total	66·13 (19·26)	63·14 (16·15)	70·82 (20·58)	65·49 (19·77)	71·33 (22·41)	68·19 (22·51)	69·96 (25·40)	68·00 (22·73)	−1·57 (−6·60 to 3·45), p=0·54	−0·29 (−6·44 to 5·86), p=0·93	0·58 (−6·57 to 7·73), p=0·87
Appearance	63·21 (22·93)	61·72 (20·68)	69·64 (23·63)	67·71 (23·62)	71·82 (24·46)	68·68 (24·77)	69·56 (27·10)	68·94 (26·26)	−0·83 (−6·57 to 4·92), p=0·78	−2·16 (−8·56 to 4·25), p=0·51	0·79 (−6·75 to 8·33), p=0·84
Visual functioning	69·75 (21·79)	62·89 (21·42)	71·91 (24·35)	64·03 (23·28)	71·63 (23·81)	68·03 (27·08)	71·57 (27·47)	67·06 (27·39)	−3·19 (−9·53 to 3·16), p=0·32	−0·69 (−6·87 to 8·25), p=0·86	−0·23 (−8·78 to 8·33), p=0·96
Clinical activity score											
Right eye	3·66 (1·28)	3·70 (1·04)	1·87 (1·31)	2·12 (1·35)	1·95 (1·55)	1·94 (1·19)	1·65 (1·46)	1·66 (1·16)	0·21 (−0·19 to 0·60), p=0·30	−0·04 (−0·49 to 0·40), p=0·84	0·00 (−0·45 to 0·45), p=1·0
Left eye	3·66 (1·28)	3·62 (1·01)	2·2 (1·34)	2·0 (1·28)	2·05 (1·49)	1·89 (1·22)	1·68 (1·25)	1·56 (1·25)	0·43 (0·01 to 0·85), p=0·047	0·05 (−0·41 to 0·50), p=0·84	0·02 (−0·41 to 0·45), p=0·93
Eyelid swelling											
Right eye									−0·11 (−0·36 to 0·14), p=1·0	−0·17 (−0·44 to 0·09), p=0·19	−0·24 (−0·51 to 0·03), p=0·077
Severe	8	9	4	6	3	2	1	0			
Moderate	30	33	20	20	19	18	20	12			
Mild	30	36	28	28	28	30	18	27			
No swelling	10	3	18	20	16	18	24	23			
Left eye									−0·04 (−0·29 to 0·21), p=0·78	−0·21 (−0·46 to 0·04), p=0·096	−0·29 (−0·55 to −0·03), p=0·027
Severe	9	8	4	7	3	2	0	0			
Moderate	30	35	21	19	20	17	22	11			
Mild	29	36	29	32	29	33	20	28			
No swelling	10	2	16	16	14	16	21	23			
Caruncle or plica swelling											
Right eye									0·06 (−0·02 to 0·13), p=0·12	0·03 (−0·05 to 0·11), p=0·44	0·05 (−0·02 to 0·12), p=0·14
Without swelling	62	69	68	67	63	62	63	62			
With swelling	16	12	2	6	3	5	4	0			
Left eye									0·03 (−0·05 to 0·12), p=0·44	0·03 (−0·03 to 0·09), p=0·28	0·07 (0·01 to 0·13), p=0·030
Without swelling	62	70	66	68	65	64	62	64			
With swelling	16	11	4	6	1	3	4	0			
Clinical severity score											
Right eye	5·62 (2·61)	5·59 (2·43)	4·49 (3·72)	4·53 (2·51)	4·49 (2·57)	4·42 (2·16)	4·56 (2·83)	4·34 (2·25)	−0·01 (−0·94 to 0·92), p=0·98	−0·24 (−0·84 to 0·37), p=0·44	−0·38 (−1·07 to 0·32), p=0·29
Left eye	5·91 (2·46)	5·69 (2·39)	4·49 (2·39)	4·67 (2·61)	4·66 (2·62)	4·51 (2·24)	4·44 (2·84)	4·26 (2·40)	0·41 (−0·22 to 1·04), p=0·20	0·014 (−0·63 to 0·66), p=0·97	−0·03 (−0·82 to 0·75), p=0·93

(Table 3 continues on next page)

	Outcome by treatment group								Adjusted mean between-group difference (95% CI), p value		
	0 weeks		12 weeks		24 weeks		36 weeks		12 weeks	24 weeks	36 weeks
	Methylpred-nisolone	Methylpred-nisolone plus mycophenolate	Methylpred-nisolone	Methylpred-nisolone plus mycophenolate	Methylpred-nisolone	Methylpred-nisolone plus mycophenolate	Methylpred-nisolone	Methylpred-nisolone plus mycophenolate			
(Continued from previous page)											
Ocular ductions (°)											
Downgaze											
Right eye	50 (45–50)	50 (45–50)	50 (40–50)	50 (45–50)	50 (49–50)	50 (42–50)	50 (50–50)	50 (45–50)	−0·22 (−2·43 to 1·99), p=0·85	−0·80 (−3·19 to 1·60), p=0·51	0·55 (−1·73 to 2·82), p=0·64
Left eye	50 (42–50)	50 (44–50)	50 (45–50)	50 (44–50)	50 (48–50)	50 (40–50)	50 (45–50)	50 (45–50)	−0·96 (−3·09 to 1·18), p=0·38	−1·31 (−3·85 to 1·23), p=0·31	2·16 (0·32 to 4·63), p=0·0087
Adduction											
Right eye	45 (40–50)	45 (40–50)	48 (40–50)	46·5 (40–50)	50 (40–50)	49 (40–50)	50 (40–50)	50 (40–50)	−0·19 (−2·17 to 1·79), p=0·85	−0·01 (−2·20 to 2·18), p=0·99	1·38 (−0·50 to 3·26), p=0·15
Left eye	45 (40–50)	48 (40–50)	50 (40–50)	47 (40–50)	50 (40–50)	48 (40–50)	50 (40–50)	50 (40–50)	−0·58 (−2·54 to 1·38), p=0·56	−0·67 (−2·92 to 1·57), p=0·55	0·68 (−1·28 to 2·63), p=0·49
Elevation											
Right eye	40 (26–50)	37·5 (19·5–50)	39·5 (25–50)	35 (20–50)	35 (25–49)	30 (20–50)	37 (25–50)	35 (22–50)	1·16 (−2·31 to 4·63), p=0·51	1·23 (−2·29 to 4·74), p=0·49	1·71 (−1·94 to 5·35), p=0·36
Left eye	35 (26–49)	35 (18–50)	35 (23–50)	35 (20–50)	35 (20–46)	35 (21–50)	37 (25–50)	35 (20–50)	3·39 (0·22 to 6·55), p=0·036	2·91 (−0·69 to 6·51), p=0·11	0·50 (−3·76 to 4·76), p=0·82
Abduction											
Right eye	40 (35–50)	40 (35–50)	40 (35–50)	40 (35–50)	40 (35–50)	40 (35–50)	40 (35–50)	35 (40–50)	0·35 (−1·84 to 2·53), p=0·75	0·48 (−1·87 to 2·84), p=0·69	1·73 (−0·63 to 4·10), p=0·15
Left eye	40 (35–50)	40 (35–50)	40 (35–50)	40 (35–50)	40 (34–50)	40 (35–50)	40 (35–50)	40 (35–50)	0·70 (−2·04 to 3·44), p=0·61	−0·31 (−3·12 to 2·49), p=0·82	0·78 (−2·23 to 3·79), p=0·61
Diplopia score	1·19 (1·04)	1·28 (1·09)	0·87 (0·99)	1·16 (1·13)	1·0 (1·14)	1·18 (1·16)	0·98 (1·12)	1·08 (1·17)	0·18 (−0·10 to 0·46), p=0·21	0·08 (−0·27 to 0·42), p=0·66	0·03 (−0·32 to 0·37), p=0·88
Thyroid-stimulating hormone receptor autoantibodies (IU/L)	8·9 (2·4–18·2)	7·2 (2·4–14·1)	8·4 (0·8–9·1)	3·5 (1·1–7·1)	4·3 (0·9–11)	2·3 (1·1–6·6)	3·6 (0·7–10·2)	2·5 (0·6–6·0)	−0·97 (−4·52 to 2·59), p=0·59	−3·49 (−7·49 to 0·51), p=0·087	−3·44 (−7·84 to 0·95), p=0·123

Data are median (IQR), mean (SD), or n, unless otherwise specified. Differences between study groups were adjusted for baseline values. Quality of life score, clinical activity score, clinical severity score, ocular duction, diplopia score or severity grade, and eyelid and cauncle swelling were prespecified outcomes, although quality of life was not part of the relevant ophthalmic composite index. The thyroid-stimulating hormone receptor autoantibodies data are post-hoc results.

Table 3: **Quality of life and ophthalmic parameters during the treatment phase and follow-up observation**

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centre trial in transplant medicine assessing patients on mycophenolate mofetil combined with ciclosporin and corticosteroids for the prevention of acute rejection, which showed that the frequency and severity of treatment-associated adverse effects are dose dependent. Our findings also support the results of the first prospective longitudinal study to investigate the tolerability and toxicity of mycophenolate in Graves' orbitopathy in accordance with the definitions of a standardised medical dictionary.[18]

The rationale for using a non-steroidal immunosuppressive agent in addition to intravenous methylprednisolone was to combine antiproliferative (mycophenolate) and anti-inflammatory (methylprednisolone) drugs, to allow the use of moderate doses of both drugs and to reduce severe treatment-associated adverse effects. Both the response rate and the number of patients with improvements were higher in the methylprednisolone plus mycophenolate group than in the monotherapy group at weeks 24 and 36. However, the relapse rate was similar between groups and the addition of mycophenolate did not prevent dysthyroid optic neuropathy or reduce the severity or magnitude of proptosis. The absence of an effect on these parameters might be because of the moderate dose of mycophenolate used, which was lower than the doses used in transplant medicine, although those higher doses are associated with much higher frequencies of adverse events.[24] On the basis of our findings, it is difficult to accept the response rate of 92·5% reported in a trial of mycophenolate (at a higher dose [1 g per day] for 24 weeks) as a monotherapy[25] in patients with Graves' orbitopathy. These results were from a single-centre, non-blinded, non-EUDRACT registered trial with an unconventional steroid regimen that did not evaluate quality of life criteria. Furthermore, in the randomisation chart, patients who did not respond to treatment were removed. These major limitations of the study design do not allow a one-to-one comparison with our trial.

In this study, dysthyroid optic neuropathy occurred in several patients in the monotherapy and combined therapy groups. However, the onset of dysthyroid optic neuropathy occurred much earlier in the monotherapy group than in the combination therapy group, in which dysthyroid optic neuropathy occurred only after the completion of methylprednisolone therapy. By comparison, in the EUGOGO intravenous methylprednisolone dose trial,[8] dysthyroid optic neuropathy was reported in all three methylprednisolone dose groups independently of the time interval and cumulative dose given. Thus, we speculate that in our trial the combination of methylprednisolone plus mycophenolate could have delayed the occurrence of dysthyroid optic neuropathy. However, after the end of the methylprednisolone therapy, the daily dose of 720 mg mycophenolate did not prevent occurrence of this outcome.

In our trial, patients with active moderate-to-severe orbitopathy, double vision (equivalent to disturbing eye motility disorders), or both, felt restricted in their daily activities and scored low on the quality of life visual functioning subscale. In previous studies,[16] quality of life correlated well with clinical severity and clinical activity of the disease, complementing the objective ophthalmic findings. In line with this observation, the quality of life visual functioning subscale in this study significantly improved within the combination group only where significant improvements of downgaze duction, elevation, and adduction were also observed. Given that the quality of life questionnaire is simple to understand, easy to complete, and disease specific, it should be used regularly as a separate outcome measurement in randomised trials in patients with Graves' orbitopathy.

Patients who responded to immunosuppressive treatment had lower baseline serum concentrations of TSHR-Ab and a longer duration of Graves' orbitopathy than did patients who did not respond to treatment. The serum titre of TSHR-Ab, especially stimulating TSHR-Ab, is a biomarker of the activity and severity of Graves' orbitopathy,[26–29] and persistently high concentrations of TSHR-Ab during the course of Graves' orbitopathy have been related to poor outcomes.[30] The presence of clinically active Graves' orbitopathy seems to be more relevant than the disease duration with respect to response to treatment.[1,5] Additionally, in patients whose orbitopathy is increasing in severity, having no deterioration might actually constitute a response. Alternatively, in patients with longer disease duration whose disease is stable or regressing, the risk of relapse might actually be lower.

The short follow-up observation period of 12 weeks is a limitation of the trial. Indeed, the longer the observation period, the better the results within the combined treatment group, thus explaining the positive post-hoc outcomes. The missing data on the need for subsequent surgical rehabilitation procedures (ie, orbital decompression, squint, and lid surgery), and the lack of placebo control are among the other main limitations of this trial. Other potential limitations are the variable numbers of participants from the different sites and the relatively long disease duration of the recruited patients. With respect to the various sites, similar results were reported for the response rates and the occurrence of dysthyroid optic neuropathy, while the duration of Graves' orbitopathy did not negatively affect response to immunosuppressive treatment in both groups.

In patients with active moderate-to-severe Graves' orbitopathy, the addition of a moderate daily oral dose of mycophenolate to an established moderate dose of intravenous methylprednisolone did not significantly affect the rate of response at 12 weeks or rate of relapse at 24 and 36 weeks. However, this add-on mycophenolate did lead to significant improvements in patients' quality of life and, in our post-hoc analysis, ophthalmic symptoms and signs.

Contributors

GJK conceived and designed the study and was the principal investigator of the clinical trial. MR (study pharmacist) coordinated the trial in all study sites, collected the raw data, and overviewed the adverse events and drug-related side effects. GJK, MR, and JK (the study's expert statistician) had full access to all raw data, analysed all findings, and take responsibility for the integrity and accuracy of the data analysis. MR, EKa, and TD set up the database and did parts of the data entry. GJK, SP, KP, EKa, EKo, AE, LCM, DF, MS, IC, DC, NC, ML, MM, FM, and CM were responsible for screening, enrolment of participants, arrangement of informed consent from the participants, provision of patient care, and documentation of study data. GJK wrote the report. LB, PP, and WMW co-designed the study, and all authors critically reviewed and approved the report.

Declaration of interests

MS received consultant fees from Roche and River Vision. PP received consultant fees from Roche, River Vision, Bayer, Navigant, and Guidepoint Global. WMW received consultant fees from Riverside. All other authors declare no competing interests.

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References

1 Wiersinga WM, Kahaly GJ (eds). Graves' orbitopathy: a multidisciplinary approach, 3rd edn. Basel: Karger, 2017.

2 Perros P, Hegedus L, Bartalena L, et al. Graves' orbitopathy as a rare disease in Europe: a European Group on Graves' Orbitopathy (EUGOGO) position statement. *Orphanet J Rare Dis* 2017; **12:** 72.

3 Bartalena L, Baldeschi L, Boboridis K, et al. The 2016 European Thyroid Association/European Group on Graves' Orbitopathy guidelines for the management of Graves' orbitopathy. *Eur Thyroid J* 2016; **5:** 9–26.

4 Bartalena L, Baldeschi L, Dickinson A, et al. Consensus statement of the European Group on Graves' orbitopathy (EUGOGO) on management of GO. *Eur J Endocrinol* 2008; **158:** 273–85.

5 Zang S, Kahaly GJ. Steroids and the immune response in Graves orbitopathy. *Immunol Endocr Metab Agents Med Chem* 2011; **11:** 90–98.

6 Suda ST, Chida K, Matsuda H, et al. High-dose intravenous glucocorticoid therapy abrogates circulating dendritic cells. *J Allergy Clin Immunol* 2003; **112:** 1237–39.

7 Kahaly GJ, Pitz S, Hommel G, Dittmar M. Randomized, single blind trial of intravenous versus oral steroid monotherapy in Graves' orbitopathy. *J Clin Endocrinol Metab* 2005; **90:** 5234–40.

8 Bartalena L, Krassas GE, Wiersinga W, et al, for the European Group on Graves' Orbitopathy. Efficacy and safety of three different cumulative doses of intravenous methylprednisolone for moderate to severe and active Graves' orbitopathy. *J Clin Endocrinol Metab* 2012; **97:** 4454–63.

9 Allison AC, Eugui EM. Mycophenolate mofetil and its mechanisms of action. *Immunopharmacology* 2000; **47:** 85–118.

10 Allison AC. Mechanisms of action of mycophenolate mofetil in preventing chronic rejection. *Transplant Proc* 2002; **34:** 2863–66.

11 Eugui EM, Allison AC. Immunosuppressive activity of mycophenolate mofetil. *Ann N Y Acad Sci* 1993; **685:** 309–29.

12 Kuhn A, Ruland V, Bonsmann G. Cutaneous lupus erythematosus: update of therapeutic options part II. *J Am Acad Dermatol* 2011; **65:** e195–213.

13 Gabardi S, Tran JL, Clarkson MR. Enteric-coated mycophenolate sodium. *Ann Pharmacother* 2003; **37:** 1685–93.

14 Bjarnason I. Enteric coating of mycophenolate sodium: a rational approach to limit topical gastrointestinal lesions and extend the therapeutic index of mycophenolate. *Transplant Proc* 2001; **33:** 3238–40.

15 Wiersinga WM, Perros P, Kahaly GJ, et al. Clinical assessment of patients with Graves' orbitopathy: the European Group on Graves' Orbitopathy recommendations to generalists, specialists and clinical researchers. *Eur J Endocrinol* 2006; **155:** 387–89.

16 Ponto KA, Hommel G, Pitz S, Elflein H, Pfeiffer N, Kahaly GJ. Quality of life in a German Graves orbitopathy population. *Am J Ophthalmol* 2011; **152:** 483–90.

17 Riedl M, Kolbe E, Kampmann E, Kramer I, Kahaly GJ. Prospectively recorded and MedDRA-coded safety data of intravenous methylprednisolone therapy in Graves' orbitopathy. *J Endocrinol Invest* 2015; **38:** 177–82.

18 Riedl M, Kuhn A, Kramer I, Kolbe E, Kahaly GJ. Prospective, systematically recorded mycophenolate safety data in Graves' orbitopathy. *J Endocrinol Invest* 2016; **39:** 687–94.

19 MSSO. MedDRA Term selection: points to consider. Release 4.6; based on MedDRA version 16.1. McLean: MedDRA Maintenance and Support Services Organization, 2013.

20 ICH. Data elements for transmission of individual case safety reports E2B. London: International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, 2001.

21 ICH. Guideline for good clinical practice E6 (R1). Geneva: International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, 1996.

22 Bartalena L, Veronesi G, Krassas GE, et al. Does early response to intravenous glucocorticoids predict the final outcome in patients with moderate-to-severe and active Graves' orbitopathy? *J Endocrinol Invest* 2017; **40:** 547–53.

23 Hardinger KL, Brennan DC, Lowell J, Schnitzler MA. Long-term outcome of gastrointestinal complications in renal transplant patients treated with mycophenolate mofetil. *Transpl Int* 2004; **17:** 609–16.

24 European Mycophenolate Mofetil Cooperative Study Group. Placebo-controlled study of mycophenolate mofetil combined with cyclosporin and corticosteroids for prevention of acute rejection. *Lancet* 1995; **345:** 1321–25.

25 Ye X, Bo X, Hu X, et al. Efficacy and safety of mycophenolate mofetil in patients with active moderate-to-severe Graves' orbitopathy. *Clin Endocrinol (Oxf)* 2017; **86:** 247–55.

26 Lytton SD, Ponto KA, Kanitz M, Matheis N, Kohn LD, Kahaly GJ. A novel thyroid stimulating immunoglobulin bioassay is a functional indicator of activity and severity of Graves' orbitopathy. *J Clin Endocrinol Metab* 2010; **95:** 2123–31.

27 Ponto KA, Kanitz M, Olivo PD, Pitz S, Pfeiffer N, Kahaly GJ. Clinical relevance of thyroid-stimulating immunoglobulins in Graves' ophthalmopathy. *Ophthalmology* 2011; **118:** 2279–85.

28 Ponto KA, Diana T, Binder H, et al. Thyroid-stimulating immunoglobulins indicate the onset of dysthyroid optic neuropathy. *J Endocrinol Invest* 2015; **38:** 769–77.

29 Kahaly GJ, Olivo PD. Graves' disease. *N Engl J Med* 2017; **376:** 184.

30 Eckstein AK, Plicht M, Lax H, et al. Thyrotropin receptor autoantibodies are independent risk factors for Graves' ophthalmopathy and help to predict severity and outcome of the disease. *J Clin Endocrinol Metab* 2006; **91:** 3464–70.