

Safety and efficacy of eculizumab in Guillain-Barré syndrome: a multicentre, double-blind, randomised phase 2 trial



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Summary

Background Despite the introduction of plasmapheresis and immunoglobulin therapy, many patients with Guillain-Barré syndrome still have an incomplete recovery. Evidence from pathogenesis studies suggests the involvement of complement-mediated peripheral nerve damage. We aimed to investigate the safety and efficacy of eculizumab, a humanised monoclonal antibody against the complement protein C5, in patients with severe Guillain-Barré syndrome.

Methods This study was a 24 week, multicentre, double-blind, placebo-controlled, randomised phase 2 trial done at 13 hospitals in Japan. Eligible patients with Guillain-Barré syndrome were aged 18 years or older and could not walk independently (Guillain-Barré syndrome functional grade 3–5). Patients were randomly assigned (2:1) to receive 4 weeks of intravenous immunoglobulin plus either eculizumab (900 mg) or placebo; randomisation was done via a computer-generated process and web response system with minimisation for functional grade and age. The study had a parallel non-comparative single-arm outcome measure. The primary outcomes were efficacy (the proportion of patients with restored ability to walk independently [functional grade ≤ 2] at week 4) in the eculizumab group and safety in the full analysis set. For the efficacy endpoint, we predefined a response rate threshold of the lower 90% CI boundary exceeding 50%. This trial is registered with ClinicalTrials.gov, number, NCT02493725.

Findings Between Aug 10, 2015, and April 21, 2016, 34 patients were assigned to receive either eculizumab ($n=23$) or placebo ($n=11$). At week 4, the proportion of the patients able to walk independently (functional grade ≤ 2) was 61% (90% CI 42–78; $n=14$) in the eculizumab group, and 45% (20–73; $n=5$) in the placebo group. Adverse events occurred in all 34 patients. Three patients had serious adverse events: two in the eculizumab group (anaphylaxis in one patient and intracranial haemorrhage and abscess in another patient) and one in the placebo group (depression). The possibility that anaphylaxis and intracranial abscess were related to eculizumab could not be excluded. No deaths or meningococcal infections occurred.

Interpretation The primary outcome measure did not reach the predefined response rate. However, because this is a small study without statistical comparison with the placebo group, the efficacy and safety of eculizumab could be investigated in larger, randomised controlled trials.

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Introduction

Guillain-Barré syndrome is an immune-mediated neuropathy and the most common cause of acute flaccid tetraplegia worldwide.¹ Strong evidence supports an autoimmune cause of the disorder. Plasma exchange, in the 1980s,² and intravenous immunoglobulin, in the 1990s,³ were shown to speed up recovery in the acute and subacute phases of the disease. However, it is still unclear whether these treatments sufficiently improve long-term outcomes in patients with Guillain-Barré syndrome. A common misconception is that the prognosis of Guillain-Barré syndrome is uniformly favourable: even if treated with plasma exchange or immunoglobulin, approximately 5% of patients die of pneumonia, pulmonary embolism,

or cardiac arrhythmia which are attributed to severe respiratory or limb muscle weakness and autonomic involvement.^{1,3–5} Up to 20% of patients cannot walk independently a year after disease onset.^{1,6} In addition to incomplete recovery of motor function, many patients have a long disease course, often with pain and fatigue.⁷ Guillain-Barré syndrome affects people of any age group⁸ and the long-lasting neurological sequelae result in great social and physical loss.⁹

More than 100 years since the first description of Guillain-Barré syndrome in 1916,¹⁰ various studies of the immunopathogenesis of Guillain-Barré syndrome have suggested that the disease encompasses a group of peripheral nerve disorders. Guillain-Barré syndrome is

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Research in context

Evidence before the study

We searched PubMed from Jan 1, 1966, to Jan 20, 2018, without language restrictions, for the terms “Guillain-Barré syndrome”, “acute inflammatory demyelinating polyneuropathy”, “acute motor axonal neuropathy”, “clinical trial”, “complement”, and “eculizumab”. We identified randomised clinical trials of eculizumab for paroxysmal nocturnal haemoglobinuria, atypical haemolytic-uraemic syndrome, age-related macular degeneration, and myasthenia gravis. There was one randomised trial for Guillain-Barré syndrome that was done in Glasgow, UK, which was planned to enrol 30 patients, but ended with only seven patients and efficacy analysis was not done. We did not find any completed randomised clinical trials of eculizumab for Guillain-Barré syndrome.

Added value of this study

This study is, to our knowledge, the first placebo-controlled randomised phase 2 trial of the safety and efficacy of

eculizumab for Guillain-Barré syndrome to have enrolled the planned numbers of patients. The results suggested that, in patients with severe Guillain-Barré syndrome, eculizumab was well tolerated and potentially improved motor function in some secondary analyses.

Implications of all the available evidence

Our findings raise the possibility that complement inhibition by eculizumab might improve long-term outcomes in patients severely affected by Guillain-Barré syndrome. However, because this is a small phase 2 study without statistical comparison with the placebo group, the effects, optimal dose, treatment duration, and indication of eculizumab need to be investigated in larger, randomised controlled trials.

currently classified into two major subtypes: the classic demyelinating form, acute inflammatory demyelinating neuropathy (AIDP); and an axonal form, acute motor axonal neuropathy (AMAN).¹¹ Advances in understanding of the pathophysiology of AMAN have revealed that the binding of antibodies against ganglioside antigens expressed on the axolemma and activation of complement lead initially to nerve conduction block and eventually to axonal degeneration. In particular, the membrane attack complex, the terminal product of complement activation, could directly cause axonal degeneration in AMAN.¹² Activation of complement and deposition of the membrane attack complex on Schwann cell membranes have also been identified in autopsies of patients with AIDP,¹³ which suggests that AIDP is caused primarily by myelin disruption. However, secondary axonal loss also frequently occurs in AIDP and is the main cause of long-lasting disability.¹⁴

Ecuzumab is a humanised monoclonal antibody that binds directly to the complement protein C5, inhibiting the formation of the membrane attack complex.¹⁵ Previous clinical trials have shown its effectiveness in complement-mediated disorders such as paroxysmal nocturnal haemoglobinuria¹⁶ and atypical haemolytic uremic syndrome.¹⁷ We aimed to investigate the efficacy and safety of eculizumab in patients with severe Guillain-Barré syndrome. Our main goal was to investigate whether the addition of eculizumab to conventional immunoglobulin therapy would lead to a clinically relevant improvement in outcome.

Methods

Study design and patients

The Japanese eculizumab trial for Guillain-Barré syndrome (JET-GBS) was an investigator-led, multicentre, double-

blind, placebo-controlled, randomised phase 2 trial done at 13 hospitals in Japan. The study consisted of three periods: screening, treatment (up to week 4), and post-treatment (up to week 24). The study was done in accordance with the ethical principles of the Declaration of Helsinki and Good Clinical Practice guidelines and was approved by the institutional review board of each participating hospital. All patients gave written informed consent before study entry. The trial protocol has been published elsewhere.¹⁸

The full list of inclusion and exclusion criteria is available in the appendix. Briefly, eligibility criteria included age 18 years or older, a diagnosis of Guillain-Barré syndrome based on the National Institute of Neurological Disorders and Stroke criteria,¹⁹ presentation within 14 days from the onset of weakness, current or planned administration of immunoglobulin, and clinical severity of Guillain-Barré syndrome classified as functional grade 4 or 5. If symptoms were progressive, patients with functional grade 3 were also enrolled; progressive symptoms were defined as clear neurological deterioration compared with the patient's condition on the previous day. The Guillain-Barré syndrome functional grade (originally termed the Hughes disability grade) was defined as follows:²⁰ 0, healthy; 1, minor symptoms or signs and able to run; 2, able to walk 5 m independently; 3, able to walk 5 m with a walker or support; 4, bed-bound or chair-bound; 5, requires assisted respiration; and 6, dead.

Exclusion criteria included treatment with plasmapheresis, evident neuropathy other than Guillain-Barré syndrome, administration of immunosuppressants within 4 weeks of providing informed consent, severe concurrent disease such as malignancy, hereditary complement deficiencies, unresolved *Neisseria meningitidis* infection or a history of meningococcal infection, and active infection that is not being treated appropriately.

See Online for appendix

Randomisation and masking

After screening, patients were enrolled by study investigators and were randomly assigned in a 2:1 ratio to receive eculizumab (Soliris, Alexion Pharmaceuticals, Washington, DC, USA) or placebo; the 2:1 ratio was chosen so we could include a comparator placebo group while maximising the number of participants receiving eculizumab. The randomisation was done centrally by an independent company (ADJUST, Sapporo, Japan) through a computer-generated process and web response system with dynamic allocation and minimisation for functional grade (3 vs 4 or 5) and age (<60 years vs ≥60 years). The study drugs were assigned and labelled with random numbers according to the randomisation table created by ADJUST personnel who were not involved in the conduct or analysis of the trial. Patients, investigators, and study staff were not able to access the table and were masked to treatment group assignment. The ADJUST personnel verified that placebo and eculizumab were indistinguishable from each other in external appearance when receiving the study drugs from Alexion. The drugs were delivered to each hospital under the responsibility of the coordinating investigator.

Procedures

During the treatment period (weeks 1–4) eculizumab (900 mg) or matching placebo was administered intravenously once per week for a total of four doses (days 1, 8, 15, and 22) in conjunction with one course of intravenous immunoglobulin (400 mg/kg daily for 5 consecutive days). The first dose of eculizumab or placebo was given before or during the immunoglobulin therapy. Terminal complement complex inhibition by eculizumab predisposes patients to infections by encapsulated bacteria, especially *N meningitidis*. Meningococcal vaccination was not done; instead, all enrolled patients received antibiotic prophylaxis against *N meningitidis* from the time of the first dose of the study drug to 8 weeks after the last administration. Treatment with rituximab, plasmapheresis, or methylprednisolone pulse therapy was prohibited throughout the trial period.

Patients were assessed by neurologists for functional grade and neurological and laboratory findings weekly during the treatment period and at weeks 6, 8, 12, 16, and 24 during the post-treatment period. Nerve conduction studies and vital capacity tests were done at weeks 4, 12, and 24. Nerve conduction studies were done in the median and ulnar nerves, and compound motor action potential amplitudes, distal latencies, motor conduction velocities, F-wave latencies, sensory nerve action potential amplitudes, and sensory conduction velocities were measured. The schedule of assessments is provided in the appendix. Additionally, patients were requested to record their functional grade score in a diary each day and to stop recording it after they had an improvement of at least one grade. If all four doses of eculizumab or placebo could not be completed because of adverse

events or other contingencies, patients remained in the trial to undergo tests and assessments on the trial schedule unless they withdrew.

Data were collected with an electronic case-report form using Medidata Rave (Medidata, Tokyo, Japan). The data were independently analysed by two biostatisticians (KN and a biostatistician at Biostatistical Research Co, Tokyo, Japan).

Outcomes

The primary efficacy outcome was the proportion of patients who reached functional grade 2 (able to walk 5 m independently) or lower by week 4 (day 29). The primary safety endpoints were the incidence and severity of adverse events during the trial. The secondary endpoints based on functional grade were the proportion of patients improving by one or more functional grade from baseline at each visit, the proportion of patients with functional grade 2 or lower at each visit, time to improvement by at least one functional grade, the proportion of patients with functional grade 1 (able to run) or 0 (healthy) at week 24, and changes from peak functional grade and functional grade at each visit up to 24 weeks. The other secondary measures were the proportions of patients with a clinically relevant improvement in the Rasch-built Overall Disability Scale score²¹ (at least 6 points increase) and the Overall Neuropathy Limitations Scale (ONLS) score (at least 1 point decrease) at each visit,²² the proportion of patients requiring ventilatory support and its duration, incidence of relapse, overall survival, and changes in grip strength (using the same Smedley-spring type hand dynamometer), manual muscle testing score (sum of the scores from 13 muscles with a total score of 65), median and ulnar nerve conduction study parameters, and vital capacity at each visit from baseline, as well as the proportion of intravenous immunoglobulin re-administration. Antiganglioside IgG antibodies (GM1, GD1a, GalNAc-GD1a, GQ1b, and the GM1/GD1a, GM1/GalNAc-GD1a, GM1/GQ1b, and GD1a/GQ1b), serum concentrations of eculizumab, and serum haemolytic activity were measured as exploratory endpoints. Pharmacodynamics and kinetics were evaluated in the first ten patients enrolled.

Statistical analysis

To estimate the effect size within each group in this randomised early phase 2 trial, we used a parallel non-comparative single-arm efficacy outcome measure. Therefore, we did not do a direct group comparison between eculizumab and placebo. We determined the sample size on the basis of analysis of our historical control data.²³ Of 62 patients with Guillain-Barré syndrome with functional grades 3–5 (22 [35%] with grade 3, 34 [55%] with grade 4, and six [10%] with grade 5), 32 (52%, 90% CI 41–62) were able to walk independently at week 4 after treatment with intravenous immunoglobulin. For the primary endpoint of efficacy in the eculizumab group, we estimated that the threshold value (the lower 90% CI

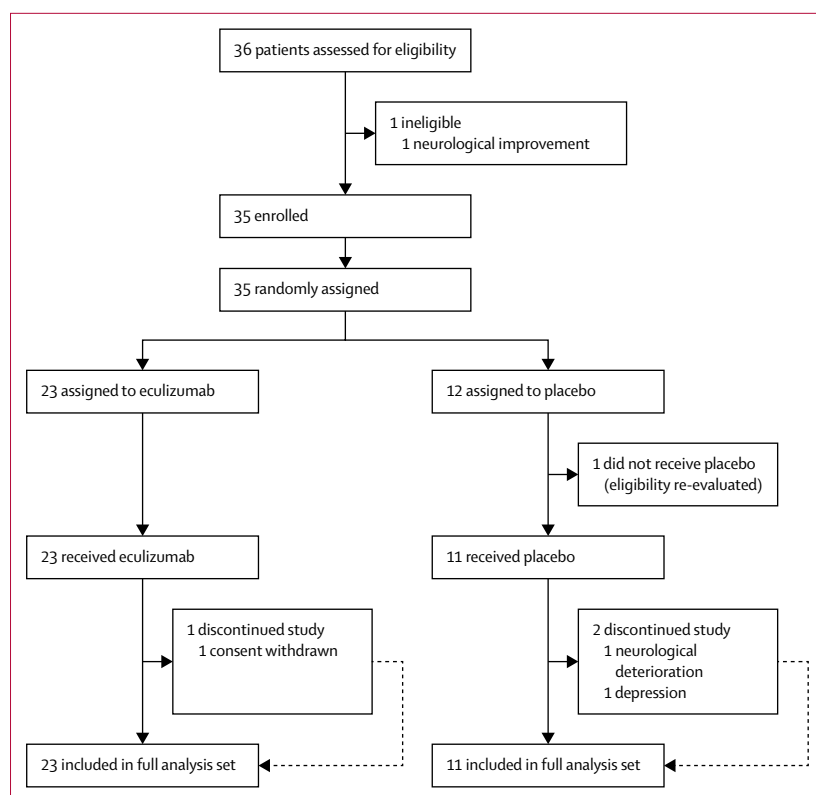


Figure 1: Trial profile

For the statistical analysis plan
see <http://opac.ll.chiba-u.jp/da/curator/104853/>

boundary) for a clinically relevant improvement would be 50% and the expected mean value 80%. The primary outcome measure was tentative because it was difficult to predict precisely the size and variability of the effect of eculizumab for Guillain-Barré syndrome. Additionally, one of the aims of this phase 2 study was to investigate optimal efficacy endpoints for future clinical trials.

A minimum sample size of roughly 20 patients in the eculizumab group would be needed to show statistical significance against our predefined threshold (at the 5% one-sided level) with at least 80% power for assessment of the response rate at week 4. To allow for a 10% dropout rate, the number of patients in the eculizumab group was increased to 22. Additionally, 11 patients were randomly assigned to the placebo group to collect efficacy and safety data and to eliminate bias. The total sample size was set at 33 patients. Because of the small sample size, the groups were not compared statistically for the primary efficacy endpoint.

The primary analyses were done in the full analysis set (ie, all patients who received their assigned drug). For the primary efficacy analysis, the exact 90% CI was calculated via the binomial distribution for the response rate of each treatment group. For sensitivity analysis, we estimated the proportions of patients achieving functional grade 2 or lower at each visit by use of the generalised linear mixed model (GLMM), to obtain point estimates and 95% CIs.

We used an unstructured matrix for the correlation, and used the Toeplitz, autoregressive, or compound-symmetry structures in order if convergence was not obtained.

For the primary safety analysis, the proportion of adverse events was estimated in each treatment group, and the exact 95% CI was calculated with the binomial distribution.

We did predefined secondary analyses with Fischer's exact test for categorical data, the GLMM for continuous data, and the Kaplan-Meier method and the Cox proportional-hazards model for time-to-event data. For predefined subgroup analysis of the efficacy outcomes, the first nerve conduction study results were used to classify patients as having AMAN or AIDP on the basis of electrodiagnostic criteria.¹¹

The proper way to address imbalance between groups and take into account baseline factors was covariate adjustment. We did post-hoc adjusted analyses for the efficacy analyses via the GLMM, with grip strength and pre-existing illness as covariates. This post-hoc adjusted analysis was a sensitivity test to justify our findings.

The significance level of primary analysis was set at 5% for a one-sided test, whereas all secondary analyses were set at 5% for two-sided tests. All statistical analyses were done with SAS version 9.4 and were described in the statistical analysis plan, which is available online and was finalised before database lock. The trial was reported to the Japanese Pharmaceuticals and Medical Devices Agency (No. 27-0613), and is registered with ClinicalTrials.gov, number NCT02493725.

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. All authors had full access to all the data in the study and the corresponding author had the final responsibility for the decision to submit for publication.

Results

Between Aug 10, 2015, and April 21, 2016, 36 patients were screened, one of whom was excluded because of neurological improvement (figure 1). The remaining 35 patients were enrolled and underwent randomisation, with 23 assigned to the eculizumab group and 12 to the placebo group. After randomisation, one patient in the placebo group improved neurologically before administration of the study drug and was thus determined to be ineligible. One patient in the eculizumab group withdrew consent and discontinued from the study during treatment, and two patients in the placebo group dropped out during the post-treatment period, one with neurological deterioration and one with depression resulting from severe disability. The last patient completed the study on Oct 5, 2016. Baseline characteristics are shown in table 1. 30 (88%) of 34 patients had a functional grade of 4 or 5, representing very severe disability. The mean time (range) from onset to intravenous immuno-

globulin administration was 5·0 days (range 2–12, SD 2·6) in the ecilizumab group and 4·6 days (2–13, 3·4) in the placebo group. The mean time from the onset of weakness to study drug administration was 6·9 days (3–12) in the ecilizumab group and 7·6 days (5–15) in the placebo group.

The proportion of patients with the primary efficacy endpoint, functional grade of 2 or less at week 4 (day 29), was 61% (90% CI 42–78; n=14) in the ecilizumab group and 45% (20–73; n=5) in the placebo group (table 2; appendix). Although the difference between groups was 15%, the lower bound of the 90% CI in the ecilizumab group was 42%, which did not exceed the predefined threshold response rate of 50%. In a sensitivity analysis using the GLMM, the adjusted proportions of patients with a functional grade of less than or equal to 2 at week 4 were 65% (95% CI 37–85) in the ecilizumab group and 45% (16–79; $p=0\cdot325$ for the difference between groups) in the placebo group (table 2).

In terms of the primary safety outcome, all patients in the ecilizumab and placebo groups reported at least one adverse event (table 3). No meningococcal infections occurred. Four serious adverse events were reported in three patients: anaphylaxis (one patient in the ecilizumab group), intracranial haemorrhage and a brain abscess (both events in the same patient in the ecilizumab group), and depression (one patient in the placebo group). Causality could not be excluded between ecilizumab and the anaphylaxis and intracranial abscess events, although the intracranial haemorrhage was considered not to be related to ecilizumab. The anaphylaxis was promptly resolved within 1 day by use of an antihistamine. The participant who had intracranial haemorrhage 5 days after the last administration of ecilizumab had pre-existing hypertension and was taking a direct oral anticoagulant. Subsequently, he had a brain abscess that occurred in the haemorrhagic focus 43 days after the bleeding (48 days after the last dose of ecilizumab). The patient was treated with antibiotics and drainage and had a full recovery by 63 days after the abscess was discovered. Adverse events that led to the discontinuation of the study medication were skin rash and anaphylaxis, both of which were in the ecilizumab group. All adverse events resolved during the study period.

Secondary endpoints are shown in table 2 and the appendix. The proportions of patients with improvement by one functional grade at weeks 4 and 24 were similar between the ecilizumab and placebo groups. By week 24, 21 (92%, 95% CI 67–98) of 22 patients in the ecilizumab group and eight (72%, 32–93) of nine patients in the placebo group achieved a functional grade of 2 or lower, and from week 4 through to week 24 the proportion of such patients was around 20% higher in the ecilizumab group than in the placebo group, but these differences were not significant (appendix). The number of days needed for improvement by one functional grade was similar between the two groups (table 2). By week 24, the

	Ecilizumab (n=23)	Placebo (n=11)
Age (years)		
Median (IQR)	56 (42–74)	59 (32–73)
Sex		
Men	16 (70%)	8 (73%)
Women	7 (30%)	3 (27%)
Antecedent illness		
None	2 (9%)	1 (9%)
Respiratory tract infection	11 (48%)	3 (27%)
Diarrhoea	12 (52%)	8 (73%)
Other	4 (17%)	2 (18%)
Days from onset to immunoglobulin administration		
Mean (range, SD)	5·0 (2·0–12·0, 2·6)	4·6 (2·0–13·0, 3·4)
Functional grade		
3 (able to walk 5 m with a walker or support)	3 (13%)	1 (9%)
4 (bed-bound or chair-bound)	19 (83%)	9 (82%)
5 (requires assisted respiration)	1 (4%)	1 (9%)
Sum scores of manual muscle testing		
Mean (SD)	41·5 (15·4)	34·0 (17·9)
Grip strength (average of both sides)		
Mean (SD)	7·21 (7·34)	3·03 (4·78)
Antiganglioside antibody		
GM1	6 (26%)	5 (45%)
Electrodiagnostic subtype		
Acute motor axonal neuropathy	13 (57%)	4 (36%)
Acute inflammatory demyelinating neuropathy	7 (30%)	7 (64%)
Unclassified	3 (13%)	0 (0%)
Data are n (%) unless noted otherwise.		

Table 1: Baseline characteristics of patients with Guillain-Barré syndrome

proportion of patients who achieved a functional grade of 1 (able to run) or 0 (healthy) was 74% (52–90; n=17) in the ecilizumab group versus 18% (2–52; n=2) in the placebo group. The mean change in functional grade from the peak to the value at week 24 was $-3\cdot0$ (SD 1·1) in the ecilizumab group and $-2\cdot1$ (1·1) in the placebo group. For the proportion of patients who achieved functional grade of 1 or lower, the between-group difference became more apparent over time up to week 24 (appendix).

The other secondary outcomes, the proportion of patients with improved Rasch-built Overall Disability Scale and ONLS scores, requirement for ventilation, duration of ventilation, incidence of relapse, overall survival, changes in grip strength, manual muscle testing scores, nerve conduction parameters, and vital capacity, and intravenous immunoglobulin re-administration, did not show any clear differences between the ecilizumab and placebo groups. Full data for the secondary outcomes are provided in the appendix.

	Ecuzumab (n=23)	Placebo (n=11)	Between-group difference (95% CI)	p value
Primary outcome				
Able to walk 5 m independently (functional grade ≤ 2)				
Week 4, % (90% CI)	61% (42 to 78)	45% (20 to 73)	15% (-20 to 51)	..
Number of patients	14/23	5/11	..	..
Secondary outcomes				
Improvement by one functional grade*†				
Week 4, % (95% CI)	66% (39 to 86)	61% (27 to 87)	5% (-31 to 40)	0.801
Patients with data	22	11	..	..
Week 24, % (95% CI)	95% (70 to 99)	91% (45 to 99)	4% (-17 to 24)	0.710
Patients with data	22	9	..	..
Able to walk 5 m independently (functional grade ≤ 2), sensitivity analysis*†				
Week 4, % (95% CI)	65% (37 to 85)	45% (16 to 79)	20% (-19 to 58)	0.325
Patients with data	22	11	..	..
Week 24, % (95% CI)	92% (67 to 98)	72% (32 to 93)	20% (-14 to 54)	0.187
Patients with data	22	9	..	..
Time to improvement by one functional grade (days)				
Median (95% CI)	19.0 (9.0 to 35.0)	22.0 (7.0 to 59.0)	-3.0‡	0.542
Patients with data	23	11	..	..
Able to run (functional grade ≤ 1)§				
Week 24, % (95% CI)	74% (52 to 90)	18% (2 to 52)	56% (27 to 85)	0.004
Number of patients	17/23	2/11	..	..
Change in functional grade from peak†				
Week 4, mean (SD)	-1.7 (1.3)	-1.1 (1.0)	-0.64 (-1.50 to 0.22)	..
Patients with data	22	11	..	..
Week 24, mean (SD)	-3.0 (1.1)	-2.1 (1.1)	-0.89 (-1.78 to 0.00)	..
Patients with data	22	9	..	..
Patients with clinically relevant improvement in Rasch-built Overall Disability Scale score†				
Week 4, % (95% CI)	77% (54.6 to 92.2)	73% (39.0 to 94.0)	4.6% (-27.1 to 36.2)	..
Number of patients	20/22	8/11	..	..
Week 24, % (95% CI)	95% (77.2 to 99.9)	100% (66.4 to 100.0)	-4.6% (-13.3 to 4.2)	..
Number of patients	21/22	9/9	..	..
Patients with decrease of ≤ 1 in Overall Neuropathy Limitations Scale score†				
Week 4, % (95% CI)	82% (60 to 95)	73% (39 to 94)	9% (-22 to 40)	..
Number of patients	18/22	8/11	..	..
Week 24, % (95% CI)	100% (85 to 100)	100% (66 to 100)	0‡	..
Number of patients	22/22	9/9	..	..
Required ventilation				
Week 4, % (95% CI)	5% (0 to 23)	9% (0 to 41)	-5% (-24 to 15)	..
Number of patients	1/22	1/11	..	..
Week 24, % (95% CI)	0% (0 to 15)	0% (0 to 34)	0‡	..
Number of patients	0/22	0/9	..	..
Duration of ventilation (days)				
Median (95% CI)	17.5 (11.0 to 31.0)	34.0 (27.0 to 41.0)	-16.5‡	0.198
Number of patients¶	4/23	2/11	..	..
Number of relapses				
Number of events	0	0	..	..
Number of deaths				

(Table 2 continues on next page)

	Ecuzumab (n=23)	Placebo (n=11)	Between-group difference (95% CI)	p value
(Continued from previous page)				
Number of events	0	0	..	..
Change in grip strength (kg)†				
Week 4, mean (SD)	9.1 (11.6)	5.0 (7.6)	4.1 (–2.8 to 11.0)	..
Patients with data	22	11	..	..
Week 24, mean (SD)	20.8 (14.9)	15.8 (10.6)	4.9 (–5.0 to 14.9)	..
Patients with data	22	9	..	..
Change in sum manual muscle testing score†				
Week 4, mean (SD)	12.3 (15.4)	13.3 (9.5)	–1.0 (–10.1 to 8.2)	..
Patients with data	22	11	..	..
Week 24, mean (SD)	20.5 (14.4)	19.8 (10.1)	0.7 (–9.2 to 10.6)	..
Patients with data	22	9	..	..
Change in nerve conduction parameter from baseline**				
Median CMAP amplitude (mV)				
Week 4, mean (SD)	0.73 (3.95)	–0.83 (5.11)	1.56 (–2.16 to 5.28)	..
Patients with data	22	11	..	..
Week 24, mean (SD)	2.15 (3.97)	2.64 (2.66)	–0.50 (–3.04 to 2.04)	..
Patients with data	22	9	..	..
Ulnar CMAP amplitude (mV)				
Week 4, mean (SD)	0.05 (2.95)	–0.78 (3.57)	0.83 (–1.80 to 3.46)	..
Patients with data	22	11	..	..
Week 24, mean (SD)	2.21 (2.86)	1.19 (3.30)	1.02 (–1.69 to 3.73)	..
Patients with data	22	9	..	..
Change in vital capacity from baseline (L)††				
Week 4, mean (SD)	0.39 (0.55)	0.45 (0.23)	–0.06 (–0.38 to 0.26)	..
Patients with data	22	11	..	..
Week 24, mean (SD)	0.74 (0.60)	0.75 (0.65)	–0.01 (–0.63 to 0.61)	..
Patients with data	22	9	..	..
Intravenous immunoglobulin re-administration, % (95% CI)	13% (3 to 34)	9% (0 to 41)	4% (–18 to 26)	1.000
Number of patients	3/23	1/11	..	..

Numbers of patients are provided for percentages calculated by dividing numerator by denominator, and numbers of patients with data are provided for other types of outcomes. p values were calculated only for the predefined group comparisons. CMAP=compound muscle action potential. *Calculated with generalised linear mixed models. †All data at each visit are available in the appendix. ‡95% CI could not be calculated. §The proportion of patients with functional grade ≤1 was evaluated only at week 24. ¶These patients needed ventilation within 4 weeks; three of the four in the ecuzumab group and one of the two in the placebo group were weaned from ventilation before week 4. ||Rates of change are shown in the appendix. **Other nerve conduction parameters are shown in the appendix. ††Results for percentage vital capacity are shown in the appendix.

Table 2: Primary and secondary outcome measures

In the predefined subgroup analyses, we detected no significant associations between positivity for anti-ganglioside antibodies and changes in functional grade (appendix). 13 patients in the ecuzumab group and four in the placebo group were diagnosed with AMAN, and seven in each group had AIDP (table 1). The electrodiagnostic subtypes were also not associated with recovery, including the proportion of patients able to walk at week 4 and able to run at week 24 (appendix). Figure 2 shows ecuzumab concentration and haemolysis activity as measured in the first ten patients (seven in the ecuzumab group and three in the control group). In the seven patients assigned to ecuzumab, the peak and

trough concentrations increased above 35 µg/mL, which was the minimum therapeutic level reported for the treatment of paroxysmal nocturnal haematuria (figure 2A),¹⁵ and complement activity, measured with haemolysis, was potently suppressed throughout the treatment period (figure 2B). In the ecuzumab group, the drug concentration markedly decreased after the first administration, suggesting substantial ecuzumab consumption by complement components (figure 2A).

In a post-hoc analysis, the mean functional grade was lower in the ecuzumab group than in the placebo group at each timepoint after treatment, and the difference in the mean values became increasingly evident from week 4 to

	Ecuzumab (n=23)	Placebo (n=11)
Any event	23 (100%)	11 (100%)
Adverse events affecting $\geq 10\%$ patients in either group		
Insomnia	6 (26%)	1 (9%)
Headache	4 (17%)	2 (18%)
Nasopharyngitis	4 (17%)	0
Constipation	4 (17%)	2 (18%)
Rash	4 (17%)	0
Myalgia	3 (13%)	1 (9%)
Nausea	3 (13%)	1 (9%)
Dyshidrotic eczema	3 (13%)	0
Oral mucositis	3 (13%)	0
Hepatic function abnormal	4 (17%)	2 (18%)
Neutrophil count decrease	3 (13%)	1 (9%)
Hyponatraemia	3 (13%)	0
Haematuria	2 (9%)	2 (18%)
Serious adverse events		
Anaphylaxis	1 (4%)	0
Intracranial haemorrhage	1 (4%)*	0
Brain abscess	1 (4%)*	0
Depression	0	1 (9%)

Data are n (%). Adverse events were coded with the preferred terms from the Medical Dictionary for Regulatory Activities. *Occurred in the same patient.

Table 3: Adverse events

week 24 (appendix). Additionally, to address imbalance between the groups, we did post-hoc adjusted analyses with grip strength and antecedent illness as covariates; the outcome measures were not affected (appendix).

Discussion

In this phase 2 trial in patients with severe Guillain-Barré syndrome, the primary outcome, the proportion of patients regaining the ability to walk by week 4, did not exceed the predefined response threshold (50%) in the ecuzumab group. Ecuzumab showed potential evidence of improving motor function in some of the secondary endpoints, although the study was not designed for statistical comparisons between the groups. The proportion of patients who regained the ability to run by week 24 was greater in the ecuzumab group than in the placebo group; this endpoint was only one of the secondary measures, but was consistent with the potential improvement in mean functional grade score from its peak to the value at week 24 in the same patients. These findings suggest that add-on ecuzumab therapy might improve outcomes in patients severely affected by Guillain-Barré syndrome who are being treated with intravenous immunoglobulin. Ecuzumab was well tolerated in most of the patients, although causality could not be ruled out for anaphylaxis and an intracranial abscess. No deaths or cases of meningococcal meningitis occurred. This study included a control group (immunoglobulin plus placebo) to allow us to estimate the effect size of ecuzumab and its standard deviation for future trials.

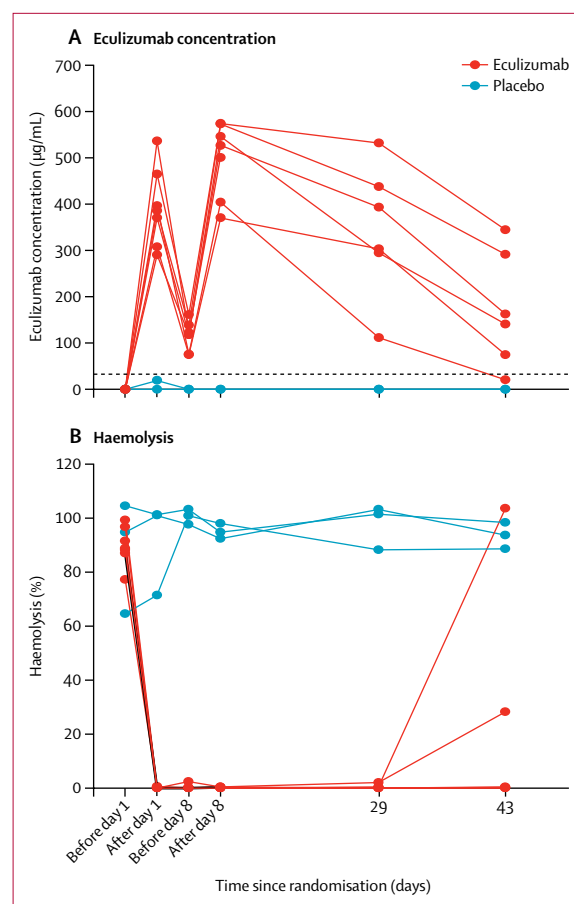


Figure 2: Ecuzumab concentration (A) and haemolysis activity (B) Measurements were made in the first ten patients enrolled in the study, of whom seven were assigned ecuzumab and three were assigned placebo. The dotted line shows 35 µg/mL, the minimum therapeutic concentration of ecuzumab reported in clinical trials for paroxysmal nocturnal haematuria.¹⁵

Guillain-Barré syndrome remains a serious disease,^{24,25} and conventional treatments are not sufficiently effective, particularly for severe Guillain-Barré syndrome.^{2,3} Over the past 20 years, several new interventions, including interferon beta-1a, brain-derived neurotrophic factor, and CSF filtration, have been tried, but did not show efficacy.²⁶

Inhibition of complement activation is a new approach for treating Guillain-Barré syndrome. Previous experimental studies in rabbit models of axonal Guillain-Barré syndrome have implicated complement-mediated axonal damage.¹² Activation of the complement pathway and subsequent formation of the membrane attack complex (C5b-9), result in changes in nerve structure and axonal degeneration.¹² In a murine model of axonal damage induced by antiganglioside antibodies, ecuzumab effectively prevented respiratory muscle paralysis and destruction of the motor nerve terminals.²⁷ Evidence from an autopsy study suggested that complement activation triggered demyelination in AIDP.¹³ Based on these

findings, the first clinical trial of eculizumab was started in Glasgow, UK, by Hugh Willison and colleagues, who did most of the preclinical studies on eculizumab.²⁷ However, the planned number of patients (n=30) was not accrued over the 2 year study period.²⁸ Instead, seven patients were enrolled, of whom five were treated with eculizumab and two with placebo, and efficacy was not analysed. Therefore, our study is, to our knowledge, the first clinical trial to enrol the planned number of patients and investigate the efficacy and safety of eculizumab therapy for Guillain-Barré syndrome.

The incidence of subtypes of Guillain-Barré syndrome varies geographically, with AIDP predominant in the European countries and AMAN more common in Asia.²⁹ Our study was based in Japan, so 50% of enrolled patients had AMAN. However, our subgroup analysis suggested that the efficacy of eculizumab did not differ among the subtypes. These findings should be evaluated in future multinational investigations.

The primary efficacy endpoint was not met, with the response rate not exceeding the predefined threshold. A possible reason for this finding could be that the study participants were more severely affected by the disease than expected. In our 62 historical controls with Guillain-Barré syndrome,²³ the proportion of patients with functional grade 3–5 who regained the ability to walk independently by week 4 was 52% (90% CI 41–62), and on the basis of these data, the response rate was tentatively set as 80%. In the present study, 88% of patients had a functional grade of 4 or 5. Our results also raise the question as to which endpoints are appropriate in clinical trials of Guillain-Barré syndrome. Over the past 30 years, trials for Guillain-Barré syndrome have investigated outcomes at 4 weeks, which reflects the speed of recovery in the acute-to-subacute phase of the disease. However, another important goal of trials investigating Guillain-Barré syndrome should be to study the effects of interventions on long-term outcomes. In this respect, we propose that the regaining of normal or nearly normal motor function (eg, patients being able to run) by week 24 might be a more appropriate endpoint. The prognosis of Guillain-Barré syndrome is determined by the extent of axonal loss in the acute phase. If axonal damage is minimised by effective treatment in that phase, sufficient nerve regeneration and collateral sprouting from surviving motor axons could be expected several months after the disease peak.

Another limitation of our study is that all patients received standard high-dose intravenous immunoglobulin therapy, so the possibility exists that eculizumab was partly neutralised by the concomitantly administered immunoglobulins. The results of our pharmacodynamic studies showed that 900 mg of eculizumab per week for 4 weeks maintained concentrations of eculizumab similar to the therapeutic levels reported for paroxysmal nocturnal haematuria,¹⁶ but it is unknown whether such concentrations are

satisfactory for complement inhibition in Guillain-Barré syndrome. Figure 2 shows noticeable consumption by complement components of eculizumab in the superacute phase of Guillain-Barré syndrome, which suggests that larger doses might be necessary to sufficiently inhibit complement activation in this syndrome. The optimal eculizumab dose should be investigated in future studies. Moreover, intravenous immunoglobulin might inhibit C3b.³⁰ In the classic complement pathway, C3 activation leads to the cleavage of C5 into C5a and C5b and the formation of C5b-9, the membrane attack complex. Therefore, the possibility that C3 inhibition by intravenous immunoglobulin reduced the formation of the membrane attack complex could not be excluded.

A further potential limitation is that the number of patients included in this preliminary study was small, and therefore we did not plan statistical comparisons between the eculizumab and placebo groups. Our results should be validated in larger studies that include statistical comparisons with the placebo group. Furthermore, electrodiagnostic classification was based on single nerve conduction study results; sequential findings should be considered in future studies. Finally, this study did not elucidate an indication for use of add-on eculizumab. A clinical prognostic scoring system for Guillain-Barré syndrome, the modified Erasmus Guillain-Barré Syndrome Outcome Score, has been proposed,³¹ and such scales might be helpful to identify subgroups of patients who should be treated with any add-on treatments.

In conclusion, eculizumab could be relatively safe and might, with further trials, be shown to be potentially beneficial in the treatment of severe Guillain-Barré syndrome. To date, treatments for Guillain-Barré syndrome have consisted of non-selective immunomodulatory interventions such as immunoglobulin therapy or plasmapheresis. Further progress in understanding the immunopathogenesis of Guillain-Barré syndrome might allow the elucidation of the major pathogenetic cascades responsible for extensive axonal degeneration, and complement C5 might be a key molecule to target. Our data suggest that terminal complement inhibition with eculizumab might have the potential to suppress complement-mediated nerve damage and safely facilitate clinical recovery in patients with severe Guillain-Barré syndrome. The efficacy and safety of eculizumab deserve further investigation in larger, multinational, randomised controlled trials.

JET-GBS Study Group

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Contributors

SM, SKuw, NY, KKat, YSa, and SKus contributed to the study concept, design, and writing of the manuscript. YSa and KN did the statistical analysis and supervised the writing of the manuscript. YSe, YI, HA, TS, TY, YN, TK, NKoh, MKa, JI, MKu, HSu, KH, NKok, TN, RM, JK, TaS, IY, HSa, MH, KKai, HT, MKad, NS, SS, JN, HN, NM, ST, JS, MT, HK, GS, MKat, RY, HY, and HO recruited patients and collected data. MKu and SKus tested the antiganglioside antibodies. All authors had full access to the data in the study and approved the final version.

Declaration of interests

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