MEET THE PROFESSOR
UPDATE IN NEUROLOGY 2017-2018
NEUROMUSCULAR DISEASE

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CONTENT

Practice changing update in common neuromuscular disease

- Anterior horn cell disease
  - Spinal muscular atrophy (SMA)
- Amyotrophic lateral sclerosis
  - Pathophysiology
  - New classification
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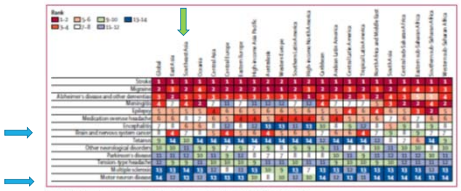
- Myasthenia gravis
  - Immunotherapy strategies
  - New drugs

Global, regional, and national burden of neurological disorders during 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015



Lancet Neurol 2017; 16: 877–97

ANTERIOR HORN CELL DISEASE

RECENT FACEBOOK FUND RAISING @ TUH

SPINAL MUSCULAR ATROPHY

TYPE	ONSET	FUNCTION	MEDIAN SURVIVAL
0	Prenatal	Respiratory failure at birth	Weeks
1	0-6 months	Never sit	<1 years
2	< 18 mounts	Sit	> 25 year
3	>18 months	Stand or ambulatory	Adult
4	30 years	Ambulatory	Adult

Treatment of infantile-onset spinal muscular atrophy with nusinersen: a phase 2, open-label, dose-escalation study

Richard S Finkel, Claudia A Chiriboga, Jiri Vajsar, John W Day, Jacqueline Montes, Darryl C De Vivo, Mason Yamashita, Frank Rigo, Gene Hung, Eugene Schneider, Daniel A Nomi, Shuting Xia, C Frank Bennett, Kathie M Bishop

Summary

Background Nusinersen is a 2′-O-methoxyethyl phosphorothioate-modified antisense drug being developed to treat spinal muscular atrophy. Nusinersen is specifically designed to alter splicing of *SMN2* pre-mRNA and thus increase the amount of functional survival motor neuron (SMN) protein that is deficient in patients with spinal muscular atrophy.

Lancet 2016; 388: 3017–26
Published Online
December 6, 2016

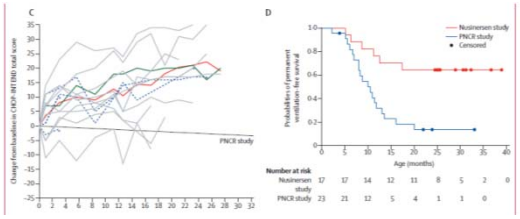
This open-label, phase 2, escalating dose clinical study assessed the safety and tolerability, pharmacokinetics, and clinical efficacy of *multiple intrathecal doses of nusinersen* (6 mg and 12 mg dose equivalents) in patients with infantile-onset spinal muscular atrophy.

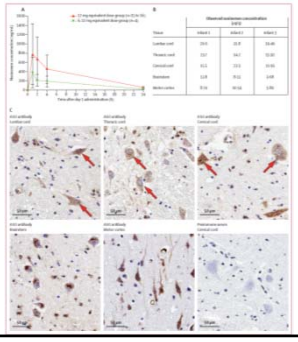
	6-12 mg group (n=4)	12 mg group (n=16)	Total (n=20)
Gender			
Male	3 (75%)	9 (56%)	12 (60%)
Female	1 (25%)	7 (44%)	8 (40%)
Race			
White	3 (75%)	13 (81%)	16 (80%)
Black	0	1 (6%)	1 (5%)
Asian	0	1 (6%)	1 (5%)
Multiple Race	1 (25%)	0	1 (5%)
Other	0	1 (6%)	1 (5%)
Weight (kg)	7·1 (5·2–8·9)	6·7 (5·1–9·3)	6·8 (5·1–9·3)
SMN2 copy number (2/3/unknown)	4/0/0	13/2/1	17/2/1
Age at symptom onset (days)	47 (28–70)	63 (21–154)	60 (21–154)
Age at diagnosis (days)	74 (42–105)	80 (0–154)	78 (0–154)
Symptom onset to enrolment (days)	97 (39–151)	77 (15–130)	81 (15–151)
Age at enrolment (days)	145 (67–207)	140 (36–210)	141 (36–210)
CHOP-INTEND score	27 (22–34)	30 (17–64)	30 (17–64)
HINE-2 score	2 (1–3)	2 (1–12)	2 (1–12)
On Bi-PAP at entry	0	0	0
Gastrostomy tube at entry	1	1	2
Ulnar CMAP amplitude (mV)	0·37 (0·20–0·60)	0·53 (0–3·20)	0·50 (0–3·20)
Peroneal CMAP amplitude (mV)	0·67 (0·30–1·40)	0·52 (0–2·70)	0·55 (0–2·70)

Data are n (%), mean (range), or n, unless otherwise stated. Bi-PAP=bi-level positive airway pressure; CHOP-INTEND=Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders. CMAP=compound muscle action potential. HINE-2=Hammersmith Infant Neurological Exam—Part 2. SMN2=Survival Motor Neuron 2.

Table 1: Demographics and baseline clinical characteristics of participants

MOTOR FUNCTION AND VENTILATOR-FREE SURVIVAL





DRUG PHARMACOKINETICS IN INFANT PLASMA, CEREBROSPINAL FLUID, AND SPINAL CORD


The New York Times

Costly Drug for Fatal Muscular Disease Wins F.D.A. Approval

"The drug, called Spinraza, will not come cheap — and, by some estimates, will be among the most expensive drugs in the world."

"Biogen, which is licensing Spinraza from Ionis Pharmaceuticals, said this week that one dose will have a list price of $125,000. That means the drug will cost $625,000 to $750,000 to cover the five or six doses needed in the first year, and about $375,000 annually after that, to cover the necessary three doses a year. Patients will presumably take Spinraza for the rest of their lives."

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Nusinersen versus Sham Control in Infantile-Onset Spinal Muscular Atrophy

CONCLUSIONS

Among infants with spinal muscular atrophy, those who received nusinersen were more likely to be alive and have improvements in motor function than those in the control group. Early treatment may be necessary to maximize the benefit of the drug. (Funded by Biogen and Ionis Pharmaceuticals; ENDEAR ClinicalTrials.gov number, NCT02193074.)

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Nusinersen Group (N = 80)	Control Group (N = 41)
Female sex — no. (%)	43 (54)	24 (59)
Age at first dose — days		
Mean	183	182
Range	51–242	59–242
Age at symptom onset — wk		
Mean	7.9	9.6
Range	2–18	3–20
Age at diagnosis of spinal muscular atrophy — wk		
Mean	12.6	17.5
Range	5–28	3–50
Disease duration at screening — wk		
Mean	13.2	13.9
Range	0–25.9	0–23.1
Symptoms of spinal muscular atrophy — no. (%)		
Hypotonia	80 (100)	41 (100)
Developmental delay of motor function	71 (89)	39 (95)
Paradoxical breathing	71 (89)	27 (66)
Pneumonia or respiratory symptoms	28 (35)	9 (22)
Limb weakness	79 (99)	41 (100)
Swallowing or feeding difficulties	41 (51)	12 (29)
Other	20 (25)	14 (34)
Use of ventilatory support — no. (%)	21 (26)	6 (15)
Use of a gastrointestinal tube — no. (%)	7 (9)	3 (10)
Total HINE-2 score‡	1.28±1.97	1.54±2.29
CHOP INTEND score‖	26.43±8.13	28.43±7.56
CMAP amplitude — mV		
Proximal	0.97±0.31	0.317±0.29
Ulnar	0.226±0.19	0.225±0.12

Table 2. Primary and Secondary End Points.*

End Point	Nusinersen Group	Control Group	Hazard Ratio (95% CI)	P Value
	no./total no. (%)			
Primary end points				
Motor-milestone response†				
Interim analysis	21/51 (41)	0/27	—	<0.001
Final analysis	37/73 (51)	0/37	—	—
No death or use of permanent assisted ventilation‡	49/80 (61)	13/41 (32)	0.53 (0.32–0.89)	0.005
Secondary end points§				
CHOP INTEND response¶	52/73 (71)	1/37 (3)	—	<0.001
No death	67/80 (84)	25/41 (61)	0.37 (0.18–0.77)	0.004
No use of permanent assisted ventilation‡	62/80 (78)	28/41 (68)	0.66 (0.32–1.37)	0.13
CMAP response‖	26/73 (36)	2/37 (5)	—	—
No death or use of permanent assisted ventilation among those with disease duration ≤13.1 wk at screening‡	30/39 (77)	7/21 (33)	0.24 (0.10–0.58)	—
No death or use of permanent assisted ventilation among those with disease duration >13.1 wk at screening‡	19/41 (46)	6/20 (30)	0.84 (0.43–1.67)	—

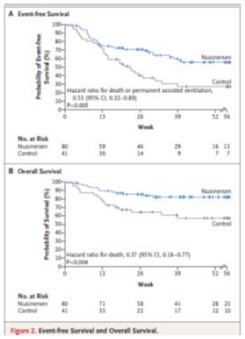


Figure 2. Event-free Survival and Overall Survival.

Table 3. Adverse Events.

Event	Nusinersen Group (N = 80)	Control Group (N = 41)
	no. (%)	
Any adverse event*	77 (96)	40 (98)
Adverse event leading to discontinuation	13 (16)	16 (39)
Severe adverse event†	45 (56)	33 (80)
Serious adverse event‡	61 (76)	39 (95)
Serious adverse event with fatal outcome‡	13 (16)	16 (39)
Respiratory disorder§	7 (9)	12 (29)
Cardiac disorder	2 (2)	3 (7)
General disorder	2 (2)	1 (2)
Nervous-system disorder	2 (2)	0

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 2, 2017 VOL. 377 NO. 18

Single-Dose Gene-Replacement Therapy for Spinal Muscular Atrophy

J.R. Mendell, S. Al-Zaidy, R. Shell, W.D. Arnold, L.R. Rodino-Klapac, T.W. Prior, L. Lowes, L. Alfano, K. Berry, K. Church, J.T. Kissel, S. Nagendran, J. L'Italien, D.M. Sproule, C. Wells, J.A. Cardenas, M.D. Heitzer, A. Kaspar, S. Corcoran, L. Braun, S. Likhite, C. Miranda, K. Meyer, K.D. Foust, A.H.M. Burghes, and B.K. Kaspar

CONCLUSIONS

In patients with SMA1, a single intravenous infusion of adeno-associated viral vector containing DNA coding for SMN resulted in longer survival, superior achievement of motor milestones, and better motor function than in historical cohorts. Further studies are necessary to confirm the safety and efficacy of this gene therapy. (Funded by AveXis and others; ClinicalTrials.gov number, NCT02122952.)

Fifteen patients with SMA1 received a single dose of intravenous adeno-associated virus serotype 9 carrying SMN complementary DNA encoding the missing SMN protein.

Three of the patients received a low dose (6.7×1013 vg per kilogram of body weight), and 12 received a high dose (2.0×1014 vg per kilogram).

- The primary outcome was safety.
- The secondary outcome was the time until death or the need for permanent ventilatory assistance.

Table 1. Demographic and Clinical Characteristics of the 15 Patients.*

Characteristic	Cohort 1 (N = 3)	Cohort 2 (N = 12)
Mean age (range) — mo	6.3 (5.9–7.2)	3.4 (0.9–7.9)
Mean weight (range) — kg	6.6 (6.0–7.1)	5.7 (3.6–8.4)
Sex — no. (%)		
Male	1 (33)	5 (42)
Female	2 (67)	7 (58)
Race — no. (%)†		
White	3 (100)	11 (92)
Other	0	1 (8)
Mean age at symptom onset (range) — mo	1.7 (1.0–3.0)	1.4 (0–3.0)
Mean age at genetic diagnosis (range) — days‡	33 (4–85)	60 (0–136)
Mean score on CHOP INTEND scale (range)§	16 (6–27)	28 (12–50)
Patients with clinical support — no. (%)		
Nutritional	3 (100)	5 (42)
Ventilatory	3 (100)	2 (17)

* Of the 15 study patients, the 3 patients in cohort 1 received a low dose of adeno-associated virus serotype 9 carrying *SMN* (6.7×10^{13} vg per kilogram) and the 12 patients in cohort 2 received a high dose (2.0×10^{14} vg per kilogram).

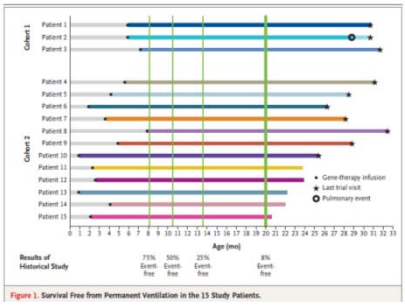


Figure 1. Survival Free from Permanent Ventilation in the 15 Study Patients.

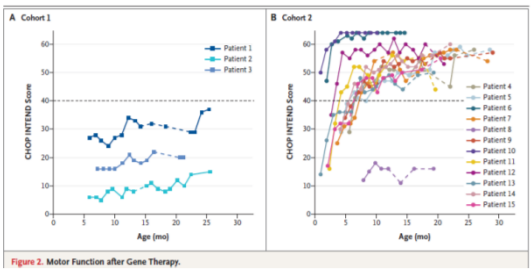


Figure 2. Motor Function after Gene Therapy.

	Placebo	Low-dose SCIg	High-dose SCIg	Overall p-value*	Low-dose SCIg vs placebo		High-dose SCIg vs placebo		High-dose SCIg vs low-dose SCIg	
					Difference	p-value†	Difference	p-value†	Difference	p-value†
Intention to treat										
Number of patients	36 (63%) [50 to 74]; n=57	22 (39%) [27 to 52]; n=57	19 (33%) [22 to 46]; n=58	0·0007	−25% (−41 to −6)	0·007	−30% (−46 to −12)	0·001	−6% (−23 to 11)	0·32
Per protocol										
Number of patients	33 (62%) [50 to 75]; n=52	21 (39%) [27 to 52]; n=54	12 (26%) [15 to 40]; n=47	<0·0001	−25% (−41 to −6)	0·01	−38% (−54 to 18)	0·0001	−12% (−30 to 5)	0·11
Relapse analysis‡										
Number of patients	32 (56%) [43·3 to 68·2]; n=57	19 (33%) [22 to 46]; n=57	11 (19%) [11 to 31]; n=58	<0·0001	−23% (−39 to 5)	0·01	−37% (−52 to −20)	<0·0001	−14% (−30 to 2)	0·06
Mixed-case analysis§										
Number of patients	34 (60%) [47 to 71]; n=57	19 (33%) [22 to 46]; n=57	14 (24%) [15 to 37]; n=58	<0·0001	−26% (−42 to −8)	0·004	−36% (−50 to −18)	0·0001	−9% (−25 to 7)	0·19
Complete case analysis¶										
Number of patients	32 (60%) [47 to 72]; n=53	19 (35%) [24 to 49]; n=54	11 (22%) [11 to 35]; n=50	<0·0001	−25% (−42 to −6)	0·008	−38% (−59·5 to −20)	<0·0001	−13% (−29 to 4)	0·10

Data are n (% [95% CI]); n or % (95% Wilson score CI). All tests are one-sided, with significance defined at a p-value of less than 0·025. SCIg=subcutaneous immunoglobulin. *Exact Cochran-Armitage test (tested for a trend with superiority of at least one IgPro20 dose to placebo). †Fisher's exact test. ‡All patients who withdrew for reasons other than relapse were assumed not to have had a relapse. §Patients who had a relapse, including those who were withdrawn because the investigator advised that the patient's safety or wellbeing could be compromised by further participation in the study or who received prohibited medication were compared with those without a relapse, including those who were withdrawn for any other reasons. ¶Patients with a relapse were compared with those without a relapse, excluding those who were withdrawn from the study.

Table 2: Primary outcome

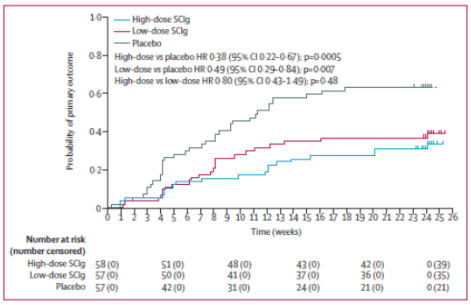
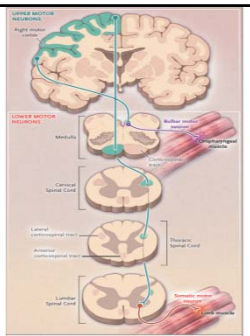


Figure 2: **Time to reach primary endpoint**
Tickmarks denote censored patients. HR=hazard ratio. SCIg=subcutaneous immunoglobulin.

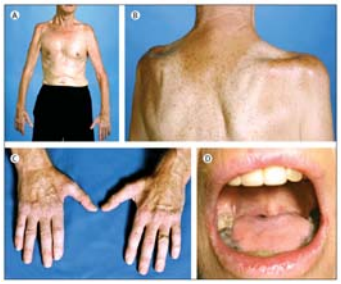
ANTERIOR HORN CELL DISEASE



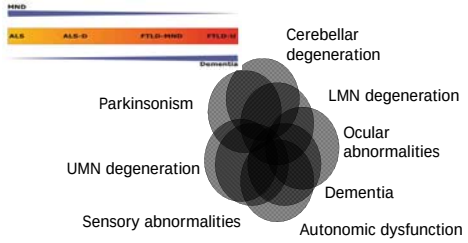
N ENGL J MED 377;2 NEJM.ORG JULY 13, 2017

Figure 1. The Motor System.
The motor system is composed of corticospinal (upper) motor neurons in the motor cortex and bulbar and spinal (lower) motor neurons, which innervate skeletal muscle.

TYPICAL ALS



ALS IS NOT JUST A DISEASE OF THE MOTOR SYSTEM



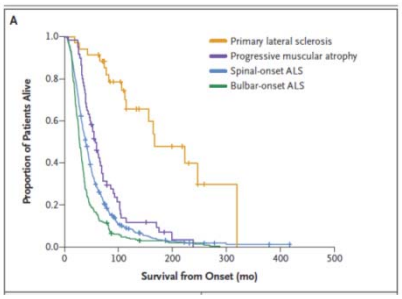


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Table 1: Summary of Revised El Escorial Research Diagnostic Criteria for ALS (Brooks et al., 2000)

The diagnosis of ALS requires:
1 Evidence of LMN degeneration by clinical, electrophysiological or neuropathological examination;
2 Evidence of UMN degeneration by clinical examination, and
3 Progressive spread of symptoms or signs within a region or to other regions, as determined by history or examination,

Together with the absence of:
[1] Electrophysiological and pathological evidence of other disease that might explain the signs of LMN and/or UMN degeneration, and

[2] Neuroimaging evidence of other disease processes that might explain the observed clinical and electrophysiological signs

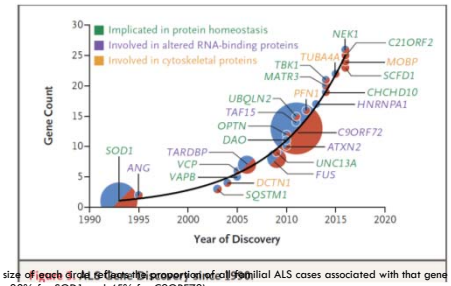
Categories of clinical diagnostic certainty on clinical criteria alone

Definite ALS
• UMN signs and LMN signs in 3 regions
Probable ALS
• UMN signs and LMN signs in 2 regions with at least some UMN signs rostral to LMN signs

Probable ALS – Laboratory supported
• UMN signs in 1 or more regions and LMN signs defined by EMG in at least 2 regions

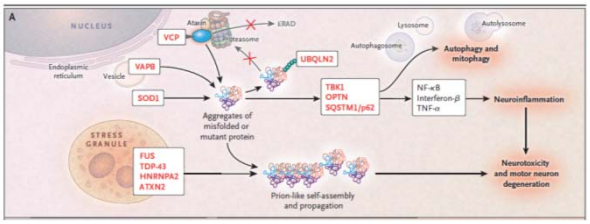
Possible ALS
• UMN signs and LMN signs in 1 region (together), or
• UMN signs in 2 or more regions
• UMN and LMN signs in 2 regions with no UMN signs rostral to LMN signs

UMN signs: clonus, Babinski sign, absent abdominal skin reflexes, hypertonia, loss of dexterity.
LMN signs: atrophy, weakness. If only fasciculation: search with EMG for active denervation.
Regions reflect neuronal pools: bulbar, cervical, thoracic and lumbosacral.

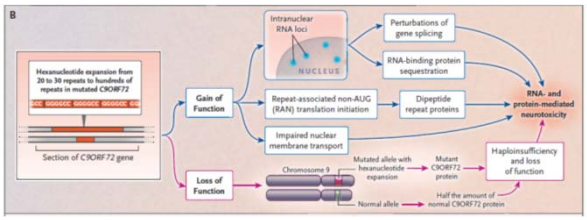


The size of each circle reflects its proportion of familial ALS cases associated with that gene (e.g., 20% for SOD1 and 45% for C9ORF72).
Blue circles indicate genes associated only with familial ALS,
Red circles indicate genes associated only with sporadic ALS,

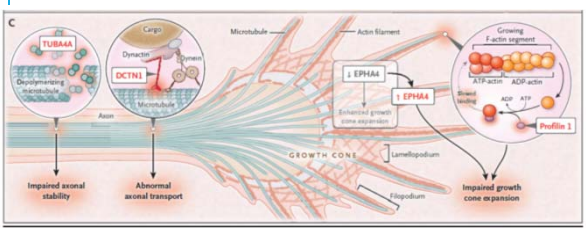
PROTEIN HOMEOSYNTHESIS



ALTERED RNA BINDING PROTEINS



CYTOSKELETON PROTEINS



Novel genes associated with amyotrophic lateral sclerosis: diagnostic and clinical implications

Ruth Chia, Adriano Chiò, Bryan J Traynor

- Familial ALS cases constitute about 10% of all cases of ALS.
- Of this 10%, about 70% can be explained by genetics.
- Two substantial increases in genetic contribution to ALS
- 2008 : TARDBP (contributes to about 4% of familial and 1% of sporadic cases)
- 2011, C9orf72 (contributing to about 40% of familial cases and 8% of sporadic cases).
- Since2014, seven novel genes—MATR3, CHCHD10, TBK1, TUBA4A, NEK1, C21orf2, and CCNF—associated with ALS have been identified

Lancet Neurol 2018; 17: 94-102

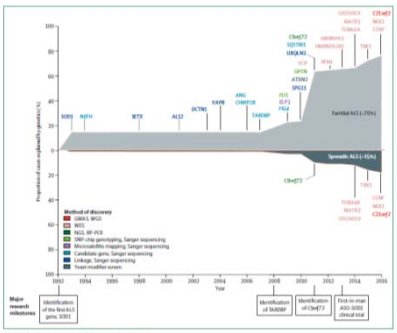


Figure 1: Genetic landscape of ALS between 1993 and 2016

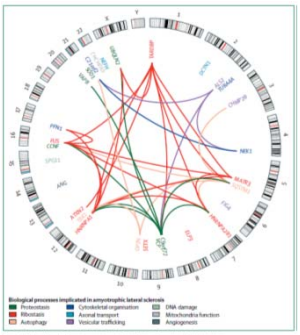


Figure 2: Interactions between genes associated with amyotrophic lateral sclerosis

Amyotrophic lateral sclerosis: moving towards a new classification system

Lancet Neurol 2016; 15: 1182–94

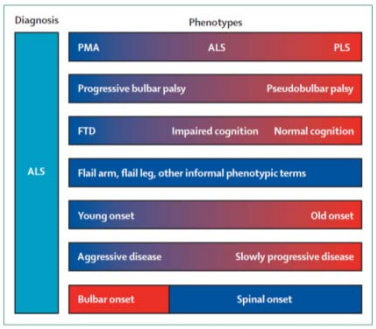


Figure 1: Diagnosis and phenotypes of amyotrophic lateral sclerosis

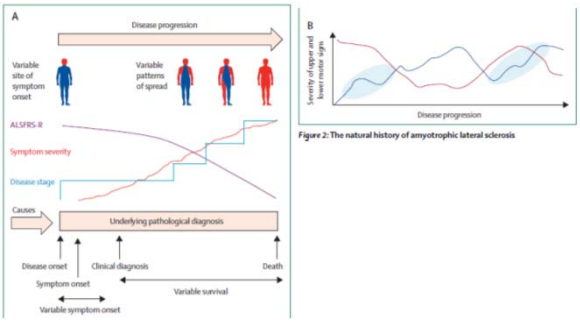


Figure 2: The natural history of amyotrophic lateral sclerosis

Panel 1: Descriptors used in amyotrophic lateral sclerosis

Extramotor features
Amyotrophic lateral sclerosis (ALS) with frontotemporal dementia, ALS dementia, parkinsonism, autonomic failure

Balance of upper and lower motor neuron involvement
Classic ALS (also known as Charcot ALS), motor neuron disease, motor system disorder, ALS, primary lateral sclerosis, progressive muscular atrophy, predominantly upper motor neuron ALS, predominantly lower motor neuron ALS, progressive bulbar palsy, pseudobulbar palsy, Mill's syndrome, El Escorial categories, flail-arm syndrome (also known as man-in-a-barrel syndrome), flail-leg syndrome (also known as syndrome polyneuritique)

Severity of symptoms
Bulbar palsy, pseudobulbar palsy, progressive bulbar palsy, bulbar ALS, flail-arm syndrome (also known as man-in-a-barrel syndrome), flail-leg syndrome (also known as syndrome polyneuritique), diaphragmatic ALS, respiratory ALS, monomelic ALS, wasted leg syndrome, El Escorial categories, clinical staging

Symmetry
Flail-arm syndrome (also known as man-in-a-barrel syndrome), flail-leg syndrome (also known as syndrome polyneuritique)

Site of onset
Bulbar onset, spinal onset, limb onset, respiratory onset

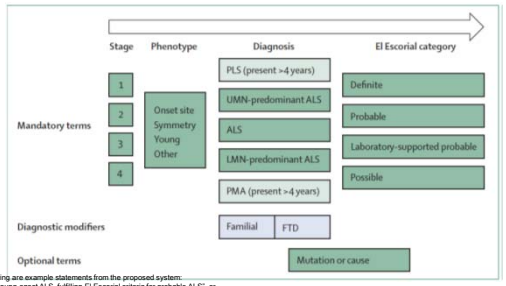
Family history
Familial ALS, sporadic ALS

Disease progression
El Escorial categories, clinical staging, functional staging, pathological staging

Age
Young-onset ALS, juvenile ALS

Prognosis
Rapidly progressive ALS, aggressive ALS, slowly progressive ALS

PROPOSED CLASSIFICATION SYSTEM FOR ALS

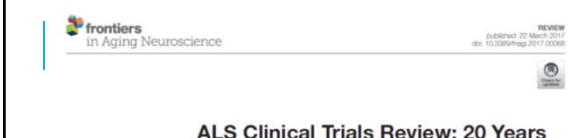


The following are example statements from the proposed system:
"Stage 2 young-onset ALS, fulfilling El Escorial criteria for probable ALS", or
"Stage 3 limb-onset UMN-predominant familial ALS secondary to *C9orf72* mutation, fulfilling El Escorial criteria for possible ALS"

	Definite ALS*	Probable ALS*	Laboratory-supported probable ALS*	Possible ALS*	Suspected ALS*
El Escorial criteria (1994)[24]	UMN and LMN signs in three regions of the body†	UMN and LMN signs in at least two regions, with some UMN signs rostral to LMN signs	–	UMN and LMN signs in only one region, or UMN signs alone in two or more regions, or LMN signs rostral to UMN signs	LMN signs only
Airlie House criteria (2000)[25]	UMN and LMN signs in the bulbar region and at least two spinal regions, or UMN signs in at least two spinal regions and LMN signs in three spinal regions	UMN and LMN signs in at least two regions, with some UMN signs rostral to LMN signs	Clinical evidence of UMN and LMN signs in only one region, or UMN signs alone in one region and electrophysiological evidence of LMN signs in at least two regions	UMN and LMN signs in only one region, or UMN signs alone in two or more regions, or LMN signs rostral to UMN signs	–
Awaji-Shima criteria (2008)[26]	Clinical or electrophysiological evidence of UMN and LMN signs in the bulbar region and at least two spinal regions, or UMN and LMN signs in three spinal regions	Clinical or electrophysiological evidence of UMN and LMN signs in at least two regions, with some UMN signs rostral to LMN signs	–	Clinical or electrophysiological evidence of UMN and LMN signs in only one region, or UMN signs alone in two or more regions, or LMN signs rostral to UMN signs	–

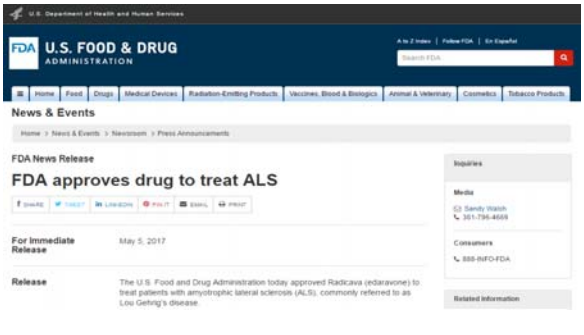
LMN=lower motor neuron. UMN=upper motor neuron. –=components are not part of the classification. *Neuroimaging and clinical laboratory studies must be done to exclude alternative diagnoses. †Regions: bulbar, cervical (corresponding to neck, arm, hand, diaphragm, and cervical spinal cord-innervated muscles), thoracic (corresponding to back and abdomen muscles), and lumbar (corresponding to back, abdomen, leg, foot, and lumbosacral spinal cord-innervated muscles).

Table 1: The El Escorial criteria and its revisions



ALS Clinical Trials Review: 20 Years of Failure. Are We Any Closer to Registering a New Treatment?

*Dmitry Petrov[1], Colin Mansfield[1], Alain Moussy[1] and Olivier Hermine[1,2,3,4,5,6,7,8]**



EDARAVARONE

Edaravone (brand names Radicava, ラジカット, Radicut) is a nootropic and neuroprotective agent used for the purpose of aiding neurological recovery following acute brain ischemia and subsequent cerebral infarction.

It acts as a potent antioxidant and strongly scavenges free radicals, protecting against oxidative stress and neuronal apoptosis

Safety and efficacy of edaravone in well defined patients with amyotrophic lateral sclerosis: a randomised, double-blind, placebo-controlled trial

Lancet Neurol 2017; 16: 505–12

The Writing Group* on behalf of the Edaravone (MCI-186) ALS 19 Study Group†

The pivotal trial grew out of a larger trial that tested edaravone's ability to slow functional decline in a larger group of ALS patients within three years of diagnosis, with forced vital capacity (FVC) of at least 70 percent of expected.

- No benefit was seen in the group as a whole.

But a post-hoc analysis suggested a slowing of decline in a subgroup of patients, those early in the disease, and with good respiratory and motor function who were nonetheless progressing.

It enrolled patients

- within two years of diagnosis,
- with FVC of at least 80 percent of expected, and
- who scored at least two points (out of a maximum of four) on each item in the ALS Functional Rating Scale-Revised (ALSFRS-R).
- The scale ranks function on 12 activities, covering bulbar, gross motor, fine motor, and respiratory function.

The first round of treatment requires a one-hour infusion every day for 14 days, followed by 14 days off. After that, the infusions are given daily for 10 out of 14 days, with 14 days off.

Observation during a 12-week pre-treatment period ensured that patients were declining prior to randomization.

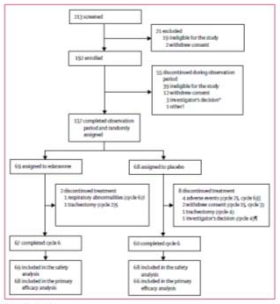


Figure 1: Trial profile

	Edaravone group (n=68)	Placebo group (n=68)
Sex		
Men	38 (55%)	41 (60%)
Women	31 (45%)	27 (40%)
Age, years	60·5 (10)	60·1 (10)
Younger than 65 years*	46 (67%)	46 (68%)
65 years or older*	23 (33%)	22 (32%)
Bodyweight, kg	57·9 (12·9)	57·8 (9·3)
Height, cm	161·8 (9·5)	162·5 (8·4)
BMI, kg/m²	21·9 (3·6)	21·8 (2·7)
ALS diagnosis		
Sporadic	68 (99%)	66 (97%)
Familial	1 (1%)	2 (3%)
ALS diagnostic criteria†		
Definite*	28 (41%)	27 (40%)
Probable*	41 (59%)	41 (60%)
ALS severity§		
Grade 1	22 (32%)	16 (24%)
Grade 2	47 (68%)	52 (76%)
Duration of disease, years	1·13 (0·5)	1·06 (0·5)
Initial symptom		
Bulbar onset	16 (23%)	14 (21%)
Limb onset	53 (77%)	54 (79%)
ALSFRS-R score		
Before observation period	43·6 (2·2)	43·5 (2·2)
At baseline (at the end of 12-week observation period)	41·9 (2·4)	41·8 (2·2)
Change about observation period		
−4 or −3*	12 (17%)	11 (16%)
−2 or −1*	57 (83%)	57 (84%)
Riluzole use		
Yes	63 (93%)	62 (91%)
No	6 (9%)	6 (9%)

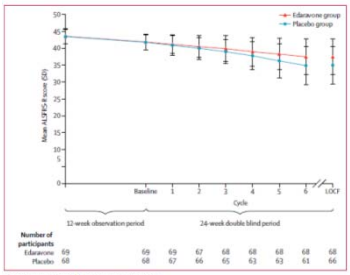


Figure 2: Mean ALSFRS-R scores during treatment

For patients with missing values at the end of cycle 6, data were imputed by the LOCF method, provided that they had completed at least cycle 3. ALS=amyotrophic lateral sclerosis. ALSFRS-R=Revised ALS Functional Rating Scale. LOCF=last observation carried forward. One patient's evaluation at the end of cycle 2 was excluded from analysis as the clinician assessing ALSFRS-R score did not have adequate training.

A reduction in ALSFRS-R decline of 33 percent.

	Least-squares mean change		Least-squares mean difference	p value*
	Edaravone (n)	Placebo (n)		
Primary endpoint				
ALSFRS-R score	−5·01, 0·64 (68)†	−7·50, 0·66 (66)†	2·49, 0·76 (0·99 to 3·98)	0·0013
Secondary endpoints				
FVC (%)	−15·61, 2·41 (67)†‡	−20·40, 2·48 (66)†	4·78, 2·84 (−0·83 to 10·40)	0·0942
Modified Norris Scale scores				
Total	−15·91, 1·97 (68)†	−20·80, 2·06 (63)†‡	4·89, 2·35 (0·24 to 9·54)	0·0293
Limb scale	−11·47, 1·61	−14·91, 1·68	3·44, 1·92 (−0·35 to 7·24)	0·0757
Bulbar scale	−4·44, 0·76	−5·89, 0·79	1·45, 0·90 (−0·23 to 3·24)	0·1092
ALSAQ-40 score	17·25, 3·39 (68)†	26·04, 3·53 (64)†‡	−8·79, 4·03 (−16·76 to −0·82)	0·0309
Grip strength (kg)§	−4·08, 0·54 (68)†	−4·19, 0·56 (66)†	0·11, 0·64 (−1·15 to 1·38)	0·8583
Pinch strength (kg)§	−0·78, 0·14 (68)†	−0·88, 0·14 (66)†	0·10, 0·16 (−0·23 to 0·42)	0·5478

Data are least-squares mean change, SE (n); or least-squares mean difference, SE (95% CI). ALS=amyotrophic lateral sclerosis. ALSAQ-40=ALS Assessment Questionnaire. ALSFRS-R=Revised ALS Functional Rating Scale. FVC=forced vital capacity (%). LOCF=last observation carried forward. *Compared between treatment groups using an ANOVA with treatment group and three dynamic allocation factors. †The numbers of patients are different from full-analysis set, because for patients with missing values at the end of cycle 6, data were imputed by the last observation carried forward (LOCF) method, provided that they had completed at least cycle 3. In the analysis of the primary outcome, patients who did not reach the end of cycle 3 (1 in the edaravone group and 2 in the placebo group) were excluded from the full-analysis set (67 in edaravone group and 68 in placebo group). ‡The numbers of patients are different from full-analysis set, because of missing data (one FVC score in edaravone group, three Modified Norris Scale scores in placebo group, and two ALSAQ-40 scores in placebo group). §Mean for the left and right hands. ALSFRS-R scores 0–48 (best). Modified Norris Scale scores 0–102 (best). Modified Norris Scale scores (Limb scale) 0–61 (best). Modified Norris Scale scores (Bulbar scale) 0–29 (best). ALSAQ-40 score 290–40 (best).

Table 2: Primary and secondary endpoints

A 2010 survey of ALS researchers identified a change of 20 percent or greater in the slope of the ALSFRS-R as "clinically meaningful."

	Adverse events		Serious adverse events	
	Edaravone group (n=69)	Placebo group (n=68)	Edaravone group (n=69)	Placebo group (n=68)
Any	58 (84%)	57 (84%)	11 (16%)	16 (24%)
Contusion	13 (19%)	9 (13%)	0	1 (2%)
Constipation	8 (12%)	8 (12%)	0	0
Dermatitis contact	8 (12%)	3 (4%)	0	0
Dysphagia	8 (12%)	10 (15%)	8 (12%)	8 (12%)
Eczema	5 (7%)	2 (3%)	0	0
Insomnia	5 (7%)	4 (6%)	0	0
Upper respiratory tract inflammation	5 (7%)	2 (3%)	0	0
Back pain	4 (6%)	1 (2%)	0	0
Headache	4 (6%)	5 (7%)	0	0
Myalgia	4 (6%)	1 (2%)	0	0
Nasopharyngitis	3 (4%)	5 (7%)	0	0
Respiratory disorder	3 (4%)	2 (3%)	2 (3%)	2 (3%)
Diarrhoea	2 (3%)	4 (6%)	0	0
Speech disorder	1 (1%)	2 (3%)	1 (1%)	2 (3%)
Pneumonia aspiration	0	2 (3%)	0	2 (3%)

Data are n (%). Includes all adverse events that had occurred in at least 5% of patients or were rated as serious adverse events in more than two patients in either treatment group during the specified study period. Adverse events were defined using the Medical Dictionary for Regulatory Activities, Japanese Version 17.0. Serious adverse events were defined as fatal, life-threatening, causing or potentially causing disability, or causing or prolonging hospitalisation.

Table 3: Adverse events

Edaravone: a new treatment for ALS on the horizon?

Criticisms

- Approval based on one Japanese study.
- Cost of treatment: estimated to be
- IV periodic infusion: adherence, inconvenience
- Long term outcome
- Benefit in specific group of patient: may not be generalizable to other ALS patients.
  Estimated to be 7%, based on ALST registry in the Netherlands and Ireland

A year's worth of treatment at the drug's current price (without consideration of insurance discounts or reimbursements) would cost approximately $146,000, according to the drug sponsor Mitsubishi Tanabe Pharma

Downloaded from http://jnnp.bmj.com/ on January 16, 2018 - Published by group.bmj.com

Neuromuscular

RESEARCH PAPER

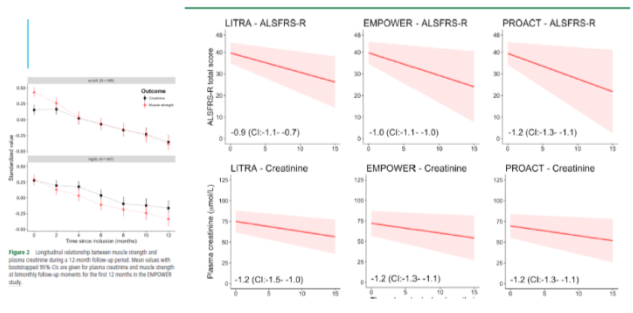
Monitoring disease progression with plasma creatinine in amyotrophic lateral sclerosis clinical trials

Ruben P A van Eijk,[1] Marinus J C Eijkemans,[2] Toby A Ferguson,[3] Stavros Nikolakopoulos,[2] Jan H Veldink,[1] Leonard H van den Berg[1]

Table 1 Baseline demographics and clinical characteristics of study participants in LITRA, EMPOWER and PRO-ACT

Demographic	LITRA (n=50)	EMPOWER		PRO ACT (n=255)
		µmol/L (n=449)	mg/dl (n=487)	
Age, years	56 (11)	57 (12)	57 (11)	57 (11)
Male	33 (66%)	285 (63%)	316 (65%)	159 (62%)
Site of symptom onset (bulbar)	13 (26%)	103 (23%)	116 (24%)	58 (23%)
Disease duration from symptom onset, months	15 (8)	15 (5)	15 (5)	15 (6)
FVC (% predicted)	99 (17)	90 (17)	88 (18)	92 (17)
ALSFRS-R	40 (5)	39 (5)	37 (6)	39 (5)
ΔFRS, months*	−0.57 (1.6)	−0.56 (1.6)	−0.68 (1.6)	−0.60 (1.6)
Plasma creatinine level (µmol/L)	74 (14)	69 (15)	72 (17)	68 (15)
Male	79 (13)	74 (15)	77 (16)	73 (15)
Female	64 (11)	60 (11)	61 (13)	61 (13)
Bulbar onset	74 (9)	71 (14)	74 (16)	69 (13)
Spinal onset	74 (15)	69 (16)	71 (17)	68 (16)
Number of follow-up measurements	5 (2)	11 (3)	10 (3)	13 (5)

Data are mean (SD) or n (%).
*ΔFRS = (ALSFRS-R score at inclusion − 48)/disease duration from symptom onset.
ALSFRS-R, amyotrophic lateral sclerosis functional rating scale–revised; FVC%, forced vital capacity.

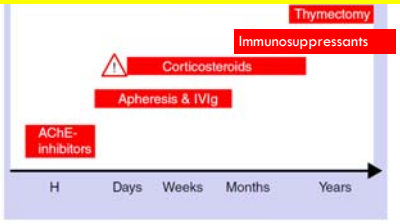


MYASTHENIA GRAVIS

Table 1. Postintervention scale.*

Response to therapy	Definition of response
Complete stable remission (CSR)	• No symptoms or signs of MG for at least 1 year and no therapy for MG during that time. • No weakness of any muscle on careful examination by someone skilled in evaluation of neuromuscular disease. • Isolated weakness of eyelid closure acceptable.
Pharmacologic remission (PR)	• Same criteria as for CSR except that some form of therapy for MG continues. • Patients taking anticholinesterase inhibitors excluded as their use suggests presence of weakness.

ONSET OF ACTION OF THE DIFFERENT THERAPY OPTIONS



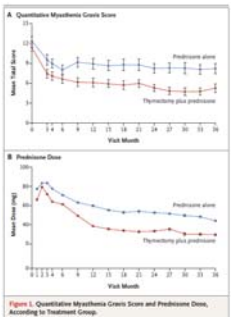
Clinical and Experimental Immunology, **175:** 408–418

Randomized Trial of Thymectomy in Myasthenia Gravis

Extended transternal thymectomy plus prednisolone vs Prednisolone alone

18-65 years old with disease duration less than 5 years, AchR antibody- positive

MGFA class II-IV (mild to severe generalized disease)



EMERGING THERAPY OPTIONS

Rituximab:
- Anti CD 20 (pre-B cell and mature B cell) – Lymphocyte depletion

Eculizumab:
- monoclonal Ab- blocks formation of terminal complement complex by selectively preventing the enzymatic cleavage of C5.

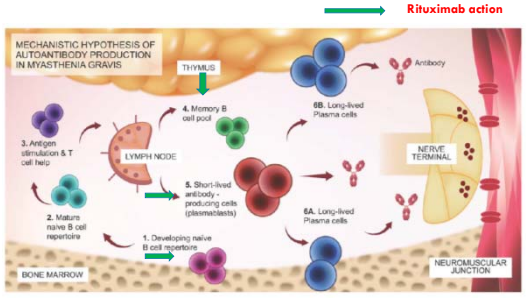
Belimumab:
- Anti B cell activating factor (BAFF-potent B cell survival factor)

Granulocyte– macrophage colony stimulating factor.

Bortezomib

Etanercept

Schematic diagram outlining the mechanistic hypothesis for the production of AChR or MuSK MG autoantibodies



INVITED REVIEW

RITUXIMAB TREATMENT OF MYASTHENIA GRAVIS: A SYSTEMATIC REVIEW

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Muscle Nerve 56: 185–196, 2017

Table 2. Demographic and clinical data from myasthenia gravis patients treated with rituximab included in the review

	All MG* (n = 169)	AChR MG (n = 99)	MuSK MG (n = 57)	*P*-value AChR vs. MuSK
Females[†]	75% (123 of 164)	69% (68 of 98)	85% (47 of 55)	0.03
Juvenile/infantile onset[‡]	18% (30 of 167)	21% (21 of 99)	13% (7 of 56)	0.18
Age of onset, years (mean ± SD, median)	36.3 ± 18.4, 35.0 (n = 159)	35.8 ± 19.7, 33.0 (n = 95)	36.5 ± 15.1, 36.0 (n = 53)	0.81
Age at rituximab treatment, years (mean ± SD, median)	44.6 ± 17.1, 45.0 (n = 166)	44.5 ± 18.3, 44.0 (n = 99)	44.0 ± 14.1, 45.0 (n = 56)	0.86
Duration, months (median, range)	60 (0–531) (n = 158)	72 (2–474) (n = 95)	60 (0–324) (n = 51)	0.32
Thymectomy	89 of 169 (53%)	58 of 99 (59%)	21 of 57 (37%)	0.009
Thymoma	16 of 169 (9%)	15 of 99 (15%)	0 of 57 (0%)	0.002
MGFA grade before rituximab (median)	IVB	IVA	IVB	0.19
Number of immunosuppressive medications before rituximab (mean ± SD)	3.6 ± 1.4 (n = 169)	3.5 ± 1.5 (n = 99)	3.9 ± 1.4 (n = 57)	0.12
Number of immunosuppressive medications immediately before rituximab (mean ± SD)	1.7 ± 0.8 (n = 136)	1.7 ± 0.9 (n = 80)	1.7 ± 0.8 (n = 46)	0.84

AChR, acetylcholine receptor; MGFA, Myasthenia Gravis Foundation of America; MuSK, muscle-specific tyrosine kinase; MG, myasthenia gravis.
[*]Four patients with multiple antibodies, 7 patients with no antibodies, and antibody status unknown in 2 patients.
[†]Gender unknown in 3 patients.
[‡]Age of onset unknown in 2 patients.

Table 3. Rituximab regimens and treatment effect in myasthenia gravis.

	All MG (n = 169)	AChR MG (n = 99)	MuSK MG (n = 57)	*P*-value AChR vs. MuSK
Rituximab induction regimen				
375 mg/m^2 per week × 4	135 of 168 (80%)	77 of 99 (78%)	48 of 57 (84%)	0.50
500 mg days 1 and 14	14 of 168 (8%)	11 of 99 (11%)	3 of 57 (5%)	
Other	19 of 168 (12%)	11 of 99 (11%)	6 of 57 (11%)	
Rituximab follow-up regimen				
Cycles of rituximab (n, % cases) (n, range of cycles)	32 of 166 (19%) (1–4)*	19 of 98 (19%) (1–2)	12 of 57 (21%) (1–4)	0.89
Infusions of rituximab (n, %) (n, range of infusions, range of intervals in months)	75 of 131 (57%) (1–8, 1–25)	46 of 79 (58%) (1–8, 1–25)	25 of 45 (56%) (1–8, 1–9)	0.77
Total number of rituximab infusions/case (initial + follow-up) (mean ± SD)	6.8 ± 3.7 (n = 167)	6.6 ± 3.3 (n = 98)	7.1 ± 4.2 (n = 57)	0.49
Treatment effect				
PIS-m MM or better (n, %)	75 of 169 (44%)	30 of 99 (30%)	41 of 57 (72%)	<0.001
PIS-m CSR or PR (n, %)	45 of 169 (27%)	16 of 99 (16%)	27 of 57 (47%)	<0.001
Any relapse after rituximab (n, %)	26 of 101 (26%)	21 of 63 (33%)	4 of 29 (14%)	0.05
Relapses after rituximab (n) (mean ± SD)	0.4 ± 0.9 (n = 100)	0.5 ± 1.0 (n = 62)	0.2 ± 0.6 (n = 29)	0.04
QMG score (mean ± SD)				
Number of cases	18	15	3	
Pre-rituximab	16.8 ± 5.5	17.7 ± 0.5	12.7 ± 4.5	0.15
Post-rituximab	8.7 ± 6.9	9.9 ± 6.7	2.3 ± 4.0	0.08
Change in score (absolute)	8.2 ± 5.1	7.7 ± 5.4	10.3 ± 2.5	0.44
Change in score (%)	52.6 ± 33.1	45.9 ± 30.9	86.3 ± 23.8	0.05

AChR, acetylcholine receptor; CSR, chronic stable remission; MM, minimal manifestations; MuSK, muscle-specific tyrosine kinase; MG, myasthenia gravis; PIS-m, postintervention scale—modified; PR, pharmacologic remission; QMG, quantitative myasthenia gravis.

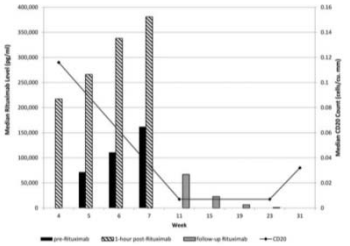

FIGURE 2. Rituximab serum levels and CD20$^+$ B-cell counts in myasthenia gravis patients before, during, and after treatment with 375-mg/m^2 rituximab infusions on weeks 4, 5, 6, and 7 (diamonds: CD20$^+$ B-cell counts)

CONCLUSION

Response predictors

- MuSK MG,
- less severe disease,
- younger age at treatment.

- Among a responder subset, 26% of AChR and 82% of MuSK MG patients showed decreased posttreatment antibody titers.
- Rituximab was generally well tolerated.
- Detectable serum rituximab and depleted CD201 B-cells were observed up to 20 and 16 weeks, respectively, after 4 weekly infusions.

Safety and efficacy of eculizumab in anti-acetylcholine receptor antibody-positive refractory generalised myasthenia gravis (REGAIN): a phase 3, randomised, double-blind, placebo-controlled, multicentre study

*James F Howard Jr, Kimiaki Utsugisawa, Michael Benatar, Hiroyuki Murai, Richard J Barohn, Isabel Illa, Saiju Jacob, John Vissing, Ted M Burns, John T Kissel, Srikanth Muppidi, Richard J Nowak, Fanny O'Brien, Jing-Jing Wang, Renato Mantegazza, in collaboration with the REGAIN Study Group**

The change in the MG-ADL score was not statistically significant between eculizumab and placebo, as measured by the worst-rank analysis. Eculizumab was well tolerated.

The use of a worst-rank analytical approach proved to be an important limitation of this study since the secondary and sensitivity analyses results were inconsistent with the primary endpoint result; further research into the role of complement is needed.

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Published Online
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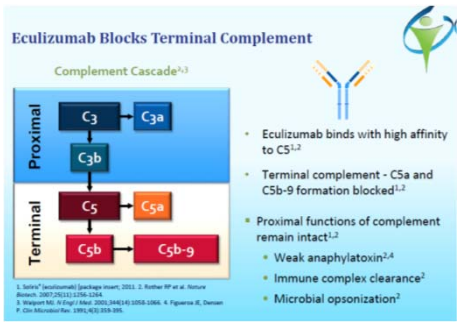
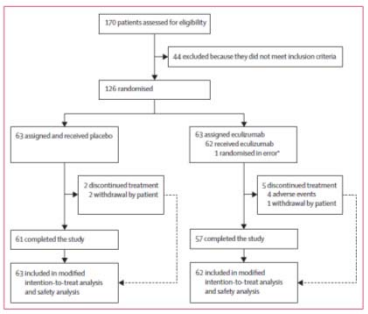
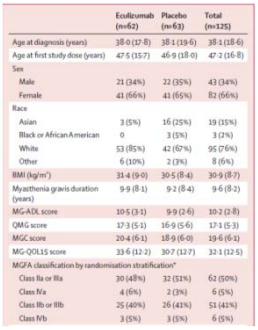
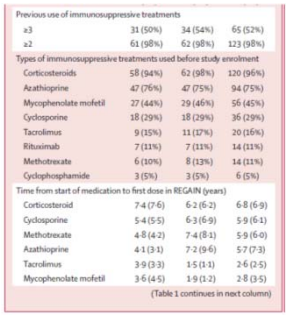




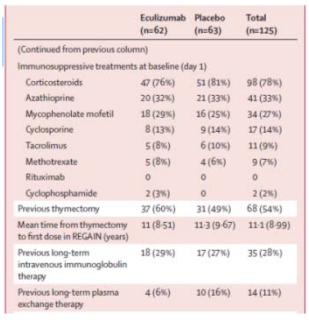


	Eculizumab (n=62)	Placebo (n=63)	Total (n=125)
Age at diagnosis (years)	38·0 (17·8)	38·1 (19·6)	38·1 (18·6)
Age at first study dose (years)	47·5 (15·7)	46·9 (18·0)	47·2 (16·8)
Sex			
Male	21 (34%)	22 (35%)	43 (34%)
Female	41 (66%)	41 (65%)	82 (66%)
Race			
Asian	3 (5%)	16 (25%)	19 (15%)
Black or African American	0	3 (5%)	3 (2%)
White	53 (85%)	42 (67%)	95 (76%)
Other	6 (10%)	2 (3%)	8 (6%)
BMI (kg/m²)	31·4 (9·0)	30·5 (8·4)	30·9 (8·7)
Myasthenia gravis duration (years)	9·9 (8·1)	9·2 (8·4)	9·6 (8·2)
MG-ADL score	10·5 (3·1)	9·9 (2·6)	10·2 (2·8)
QMG score	17·3 (5·1)	16·9 (5·6)	17·1 (5·3)
MGC score	20·4 (6·1)	18·9 (6·0)	19·6 (6·1)
MG-QOL15 score	33·6 (12·2)	30·7 (12·7)	32·1 (12·5)
MGFA classification by randomisation stratification*			
Class IIa or IIa	30 (48%)	32 (51%)	62 (50%)
Class IVa	4 (6%)	2 (3%)	6 (5%)
Class IIb or IIIb	25 (40%)	26 (41%)	51 (41%)
Class IVb	3 (5%)	3 (5%)	6 (5%)

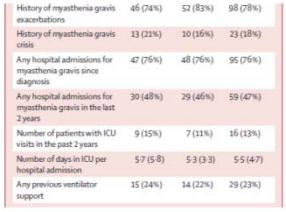


Previous use of immunosuppressive treatments			
≥3	31 (50%)	34 (54%)	65 (52%)
≥2	61 (98%)	62 (98%)	123 (98%)
Types of immunosuppressive treatments used before study enrolment			
Corticosteroids	58 (94%)	62 (98%)	120 (96%)
Azathioprine	47 (76%)	47 (75%)	94 (75%)
Mycophenolate mofetil	27 (44%)	29 (46%)	56 (45%)
Cyclosporine	18 (29%)	18 (29%)	36 (29%)
Tacrolimus	9 (15%)	11 (17%)	20 (16%)
Rituximab	7 (11%)	7 (11%)	14 (11%)
Methotrexate	6 (10%)	8 (13%)	14 (11%)
Cyclophosphamide	3 (5%)	3 (5%)	6 (5%)
Time from start of medication to first dose in REGAIN (years)			
Corticosteroid	7·4 (7·6)	6·2 (6·2)	6·8 (6·9)
Cyclosporine	5·4 (5·5)	6·3 (6·9)	5·9 (6·1)
Methotrexate	4·8 (4·2)	7·4 (8·1)	5·9 (6·0)
Azathioprine	4·1 (3·1)	7·2 (9·6)	5·7 (7·3)
Tacrolimus	3·9 (3·3)	1·5 (1·1)	2·6 (2·5)
Mycophenolate mofetil	3·6 (4·5)	1·9 (1·2)	2·8 (3·5)

(Table 1 continues in next column)



	Eculizumab (n=62)	Placebo (n=63)	Total (n=125)
(Continued from previous column)			
Immunosuppressive treatments at baseline (day 1)			
Corticosteroids	47 (76%)	51 (81%)	98 (78%)
Azathioprine	20 (32%)	21 (33%)	41 (33%)
Mycophenolate mofetil	18 (29%)	16 (25%)	34 (27%)
Cyclosporine	8 (13%)	9 (14%)	17 (14%)
Tacrolimus	5 (8%)	6 (10%)	11 (9%)
Methotrexate	5 (8%)	4 (6%)	9 (7%)
Rituximab	0	0	0
Cyclophosphamide	2 (3%)	0	2 (2%)
Previous thymectomy	37 (60%)	31 (49%)	68 (54%)
Mean time from thymectomy to first dose in REGAIN (years)	11 (8·51)	11·3 (9·67)	11·1 (8·99)
Previous long-term intravenous immunoglobulin therapy	18 (29%)	17 (27%)	35 (28%)
Previous long-term plasma exchange therapy	4 (6%)	10 (16%)	14 (11%)



History of myasthenia gravis exacerbations	46 (74%)	52 (83%)	98 (78%)
History of myasthenia gravis crisis	13 (21%)	10 (16%)	23 (18%)
Any hospital admissions for myasthenia gravis since diagnosis	47 (76%)	48 (76%)	95 (76%)
Any hospital admissions for myasthenia gravis in the last 2 years	30 (48%)	29 (46%)	59 (47%)
Number of patients with ICU visits in the past 2 years	9 (15%)	7 (11%)	16 (13%)
Number of days in ICU per hospital admission	5·7 (5·8)	5·3 (3·3)	5·5 (4·7)
Any previous ventilator support	15 (24%)	14 (22%)	29 (23%)

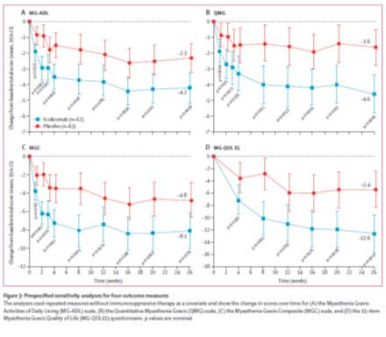
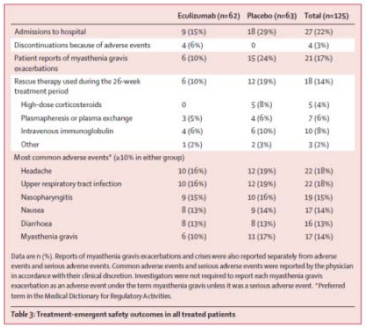


Figure 2: Prespecified sensitivity analyses for four outcome measures

The analyses used repeated measures without immunosuppressive therapy as a covariate and show the change in scores over time for (A) the Myasthenia Gravis Activities of Daily Living (MG-ADL) scale, (B) the Quantitative Myasthenia Gravis (QMG) scale, (C) the Myasthenia Gravis Composite (MGC) scale, and (D) the 15-item Myasthenia Gravis Quality of Life (MG-QOL15) questionnaire. p values are nominal.



	Eculizumab (n=62)	Placebo (n=63)	Total (n=125)
Admissions to hospital	9 (15%)	18 (29%)	27 (22%)
Discontinuations because of adverse events	4 (6%)	0	4 (3%)
Patient reports of myasthenia gravis exacerbations	6 (10%)	15 (24%)	21 (17%)
Rescue therapy used during the 26-week treatment period	6 (10%)	12 (19%)	18 (14%)
High-dose corticosteroids	0	5 (8%)	5 (4%)
Plasmapheresis or plasma exchange	3 (5%)	4 (6%)	7 (6%)
Intravenous immunoglobulin	4 (6%)	6 (10%)	10 (8%)
Other	1 (2%)	2 (3%)	3 (2%)
Most common adverse events* (≥10% in either group)			
Headache	10 (16%)	12 (19%)	22 (18%)
Upper respiratory tract infection	10 (16%)	12 (19%)	22 (18%)
Nasopharyngitis	9 (15%)	10 (16%)	19 (15%)
Nausea	8 (13%)	9 (14%)	17 (14%)
Diarrhoea	8 (13%)	8 (13%)	16 (13%)
Myasthenia gravis	6 (10%)	11 (17%)	17 (14%)

Data are n (%). Reports of myasthenia gravis exacerbations and crises were also reported separately from adverse events and serious adverse events. Common adverse events and serious adverse events were reported by the physician in accordance with their clinical discretion. Investigators were not required to report each myasthenia gravis exacerbation as an adverse event under the term myasthenia gravis unless it was a serious adverse event. *Preferred term in the Medical Dictionary for Regulatory Activities.

Table 3: Treatment-emergent safety outcomes in all treated patients

	Eculizumab (n=62)	Placebo (n=63)	Total (n=125)
Patients with any treatment-emergent serious adverse event*	9 (15%)	18 (29%)	27 (22%)
Myasthenia gravis	5 (8%)	8 (13%)	13 (10%)
Pyrexia	2 (3%)	0	2 (2%)
Upper respiratory tract infection	0	2 (3%)	2 (2%)
Apnoea	0	1 (2%)	1 (1%)
Bacteraemia	1 (2%)	0	1 (1%)
Acute cholecystitis	0	1 (2%)	1 (1%)
Deep vein thrombosis	0	1 (2%)	1 (1%)
Diverticulitis	1 (2%)	0	1 (1%)
Endocarditis	1 (2%)	0	1 (1%)
Gastritis	0	1 (2%)	1 (1%)
Gastroenteritis	0	1 (2%)	1 (1%)
General physical health deterioration	0	1 (2%)	1 (1%)
Hyperglycaemia	0	1 (2%)	1 (1%)
Intentional overdose†	0	1 (2%)	1 (1%)
Intestinal perforation	1 (2%)	0	1 (1%)
Lymphocyte count decreased	0	1 (2%)	1 (1%)
Lymphopenia	1 (2%)	0	1 (1%)
Metastases to bone	1 (2%)	0	1 (1%)
Myasthenia gravis crisis	1 (2%)	0	1 (1%)
Prostate cancer	1 (2%)	0	1 (1%)
Pulmonary embolism	0	1 (2%)	1 (1%)
Tonsillitis	0	1 (2%)	1 (1%)
Bacterial urinary tract infection	0	1 (2%)	1 (1%)
Varicella	0	1 (2%)	1 (1%)

Data are n (%). Serious adverse events were reported by the physician in accordance with their clinical discretion. Investigators were not required to report each myasthenia gravis exacerbation as an adverse event under the term myasthenia gravis unless it was a serious adverse event. *Preferred term in the Medical Dictionary for Regulatory Activities. †Overdose on concomitant medications (pyridostigmine and paracetamol); no unintentional overdoses were reported as serious adverse events.

Table 2: Serious treatment-emergent adverse events in all treated patients

FDA APPROVED ECULIZUMAB FOR THE TREATMENT OF PATIENTS WITH GENERALIZED MG

October 23, 2017

First FDA-approved treatment in more than 6 years for adult GMG patients.

- Previously failed immunosuppressive treatment and continued to suffer from significant unresolved disease symptoms.

Also approved in Europe (EU) and Japan for refractory GMG in anti AchR antibody – positive patients

For nonsteroidal IS agents, once treatment goals have been achieved and maintained for 6 months to 2 years, the IS dose should be tapered slowly to the minimal effective amount.

Dosage adjustments should be made no more frequently than every 3–6 months

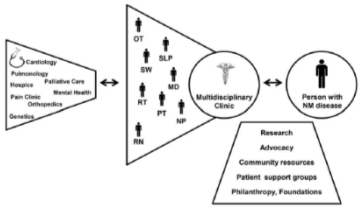
Tapering of IS drugs is associated with risk of relapse, which may necessitate upward adjustments in dose.

The risk of relapse is higher in patients who are symptomatic, or after rapid taper.

It is usually necessary to maintain some immunosuppression for many years, sometimes for life.

Neurology® 2016;87:419-425

MULTIDISCIPLINARY NETWORK OF CARE FOR PEOPLE WITH NEUROMUSCULAR DISEASE



INVITED REVIEW

DEVELOPING MULTIDISCIPLINARY CLINICS FOR NEUROMUSCULAR CARE AND RESEARCH

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Accepted 16 June 2017

Yet, multidisciplinary care requires substantial commitment of staff time and resources.

We calculated personnelcosts in our ALS clinic in 2015 and found an average cost per patient visit of $580, of which only 45% was covered by nsurance reimbursement.

MUSCLE & NERVE November 2017

Table 1. Typical schedule of multidisciplinary assessments and possible interventions for a child with muscular dystrophy.

Specialty	Frequency	Assessment	Interventions
Neurology	Twice a year	Diagnosis; medications; anticipatory guidance; coordination of care	Corticosteroids; anti-epileptic drugs
Pulmonary	Twice a year	Pulmonary function tests; chest X-ray; sleep study	Flu vaccine; nebulizer/inhalers; cough assist device; non-invasive and invasive ventilation
Cardiology	Once a year, PRN	Echocardiogram; electrocardiogram	Medications for cardiomyopathy and/or arrhythmia
Endocrinology	Once a year, PRN	Growth; bone health; steroid withdrawal/stress dose	Calcium; vitamin D; bisphosphonates
Orthopedic surgery	Once a year	Spine films; bone X-rays; MRI	Scoliosis management; ankle/joint surgery
Physical therapy and occupational therapy	Twice a year in clinic and PRN in the community	Functional evaluation; ongoing treatment	Stretching; strengthening; mobility evaluation; equipment need assessment
Wheelchair/mobility clinic and DME providers	PRN	Assistive/adaptive device assessment	Stroller; power wheelchair; shower chair; transfer devices and lifts; hospital bed
Brace clinic (orthotist)	PRN	Bracing needs evaluation	AFOs; back brace; cervical collar
Gastroenterology, speech therapy and nutrition	Once a year	Weight; swallowing; constipation/bowel function; GERD	Swallow evaluation; bowel regimen; GI prophylaxis; feeding tube
Genetics	At diagnosis and PRN	Consultation; genetic tests	Genetic counseling
Psychiatry and neuropsychology	At baseline and PRN	Consultation	Individualized education and behavioral plan; stimulants; SSRIs
Social work	Twice a year	Psychosocial support	Counseling; care coordination
Anesthesia	PRN	Pre-procedural assessment of malignant hyperthermia risk	Prevent and treat malignant hyperthermia; pain management
Palliative care and hospice	PRN	Consultation	Pain management; advanced directives; end-of-life care; bioethics

AFO, ankle-foot orthosis; DME, durable medical equipment; GERD, gastroesophageal reflux disease; GI, gastrointestinal; MRI, magnetic resonance imaging; PRN, pro re nata (i.e., "as needed"); SSRI, selective serotonin reuptake inhibitor.

Table 2. Beyond the clinic walls.

Modality	Role
Telehealth	Replace in-person visits, reduce travel efforts and costs, maintain connection with people who have lost ability to travel to clinic
Mobile health	Allow for real-time access to clinic staff using relatively low-cost technology, dedicated apps can provide patients with information or monitor function in the patient's environment
Remote monitoring platforms	Remote monitoring of well-being based on information from treatment devices (e.g., data collected by non-invasive or invasive ventilation machines, data collected from eye-gaze or communication platforms, or other connected devices)
Patient support groups	Loaner closets, peer-to-peer support groups, funding for research and clinical care
Advocacy groups	Raise awareness about the disease, fundraising, advocate for policy changes
Philanthrophy (foundations, private donors)	Provide or help raise funding for research and clinical care
Newsletters/websites	Raise awareness about the disease and treatment and research options
Patient portal	Online access to one's own clinical and research information

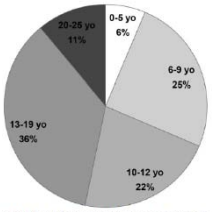

FIGURE 3. Age distribution of patients seen at the Massachusetts General Hospital pediatric multidisciplinary neuromuscular

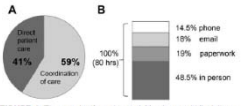

FIGURE 4. Time study of nursing activities in a multidisciplinary ALS clinic. Data on nursing staff efforts to support 3 physicians

THE CHALLENGE AHEAD

NEUROLOGIC agents are among the most expensive drugs approved in the last few years.