Table 2 GAA activity, glycogen content, and clinical outcomes

Patient	CRIM status	Age at first infusion (mo)	Age at study end (death; mo)[a]	GAA activity (nmol/h/g tissue)		Change in glycogen content[c]	Ventilation status[d]		Motor outcomes at end of study[e]	Measurable motor gains	Baseline/ screening LVM *Z* score	Week 52 (Week 104) LVM *Z* score[f]	Change in LVM *Z* score	PEDI number of domains with gains
				Baseline	Week 52 (Week 12)[b]		Baseline	End of study						
420	−	3.7	*27.1*	NAV	91.2	Increased	Noninv	*Deceased*	Sitting	Yes	7.6	7.2	−0.4	1
409	+	6.3	*7.7*	BQL	[f]	[f]	None	*Deceased*	MMF	No	8.5			NAV
413	+	7.0	43.5	BQL	153.9	Increased	None	Inv	Sitting	Yes	7.7	*0.8*	−6.9	3
412	+	8.0	*14.4*	BQL	*110.8*	*Stable*	None	*Deceased*	Sitting w/s	No	7.7	4.5	−3.2	0
404	+	8.2	47.8	8.9	132.6	Stable	None	Inv	Sitting	Yes	10.0	2.0	−8.0	3
407	−	8.2	*11.7*	BQL	*35.9*	*Stable*	None	*Deceased*	Sitting w/s	No	7.6			1
418	+	8.4	34.7	9.3	99.1	Decreased	None	None	Walking	Yes		−1.1		1
419	+	9.0	*9.1*	ND	[f]	[f]	None	*Deceased*	[f]	No	7.8			1
421	+	9.3	35.5	18.7	*98.3*	*Stable*	None	Inv	MMF	No	4.4	1.5	−2.9	1
411	+	9.8	46.9	4.8	63.3	Stable	Noninv	Inv	Sitting	Yes	8.8	5.5	−3.3	3
405	+	13.0	*17.3*	BQL	[f]	[f]	Inv	*Deceased*	MMF	No				1
417	+	14.3	42.8	31.5	48.8	Increased	None	None	Walking	Yes	7.8	3.2	−4.6	3
415	+	15.0	49.3	16.8	72.9	Decreased	None	None	Sitting	Yes	3.1	0.8	−2.3	3
406	+	16.2	54.7	9.3	59.6	Stable	Inv	Unchanged	Sitting w/s	Yes	8.8	6.9	−1.9	3
402	+	17.0	55.7	12.1	101.1	Decreased	None	None	Walking	Yes	2.9	1.1	−1.8	3
422	+	17.8	43.3	14.4	110	Increased	None	None	Walking	Yes	1.7	1.0	−0.7	2
416	+	18.1	52.6	7.2	*33.4*[g]	*Decreased*	Inv	Unchanged	MMF	No	6.3	*0.9*	−5.4	3
414	+	24.1	36.1	28	86.5	Decreased	None	None	Walking	Yes	2.3	1.4	−0.9	3
410	+	36.6	74.4	19.8	44.6	Decreased	Inv	Inv, decreased[h]	Sitting	Yes	7.3	2.8	−4.5	0
403	+	37.3	76.1	NAV	*69*	NAV	Inv	Unchanged	Sitting	Yes	5.4	2.6	−2.8	NAV
408	+	43.1	80.3	23.2	105.4	Decreased	None	None	Sitting	Yes	6.6	1.3	−5.3	2

[a]If patient died before end of study, age at death is given in italics.
[b]Week 52 value is given if available, otherwise week 12 value is given in italics.
[c]Change is from baseline to Week 52 or last assessment (Week 12, in italics). Meaningful biochemical change was defined as >20% from baseline to account for assay variability. Results within 20% of baseline were considered stable.
[d]Invasive ventilator use included ventilation via endotracheal tube or tracheostomy; noninvasive ventilator use included positive pressure ventilation applied through a nosepiece or a facemask.
[e]Motor status was determined by assessment of motor milestones.
[f]Patient died before repeat assessment.
[g]Patient 2–16 had a compromised sample at Week 52.
[h]Patient 2–10 decreased ventilator dependency from 24/24 hours to 12/24 hours by Week 104.
[i]Medians are calculated only for available values; week 52 medians include only values for samples taken at week 52.
Inv, invasive; Noninv, noninvasive; NAV, results not available; MMF, minimal motor function; ND, not done; BQL, below quantifiable levels; w/s, with support.

Table 3 Survival estimates for patients aged ≤12 mo and >12 mo at first infusion compared with survival in the untreated reference cohort

	Study patients			Untreated reference cohort	
Age category (mo)[a]	*N*	Median age at first infusion (mo)	104-week survival estimate[b]	*N*	Conditional 104-week survival estimate[b,c]
≤12	10	8.2	50.0% (19.0%, 81.0%)	59	9.2% (1.5%, 16.8%)
>12	11	17.8	90.9% (73.9%, 100.0%)	11	45.5% (16.0%, 74.9%)
All patients	21	13.0	71.1% (51.6%, 90.6%)	19	26.3% (6.5%, 46.1%)

[a]Age category is age at first infusion for study patients and age at death for the reference cohort.
[b]The Kaplan-Meier method was used to compute nonparametric estimates of the survival distribution. Values are estimate and 95% CI.
[c]Conditional survival estimates in the reference cohort were based on median age at first infusion for the corresponding study subpopulation (e.g., 104-week conditional survival rate corresponded to survival rate at 8.2 + 24 = 32.2 mo of age for the ≤12-mo category).

Table 4 Survival and ventilator-free survival in patients treated with alglucosidase alfa compared with the untreated reference cohort (*N* = 21, treated patients; *N* = 84, reference cohort)

End point	Treatment effect hazard ratio	95% confidence interval	*P*	Risk reduction
Survival	0.209	0.083–0.524	0.0009	79%
Invasive ventilator-free survival	0.421	0.202–0.876	0.0207	58%
Any ventilator-free survival	0.533	0.247–1.150	0.1088	47%

Results are from a Cox proportional hazards regression analysis which includes treatment as a time-varying covariate, and also includes age of diagnosis and age at symptom onset. Analysis is from time of diagnosis through the end of study.

Table 5 Cardiac status by echocardiography

	Baseline		Week 52		Week 104		Mean change from baseline to week 104	
Measure	*n*	Mean ± SD	*n*	Mean ± SD	*n*	Mean ± SD	*n*	% Change
LVMI	19	193.8 ± 98.5	13	89.3 ± 58.8	10	53.1 ± 13.9	9	−62.7
LVM *Z* score	19	6.5 ± 2.6	13	2.7 ± 2.5	10	0.9 ± 0.8	11	−5.3
Shortening fraction	21	35.6 ± 12.1	13	45.5 ± 5.6	10	43.8 ± 6.5	10	30.4

started below the third percentile in height and remained at a consistent height percentile throughout the study; this patient's age-equivalent weight increased from percentile 1.3 to 7.7 over the same time period. One patient died before any repeat growth assessment.

Cognitive function

Eighteen of 19 patients with follow-up data showed improvements in age-equivalent BSID-II scores from baseline to last assessment. The one patient who failed to demonstrate consistent improvement in BSID-II (and Pompe PEDI) scores to study end also experienced significant motor function loss after 1 year of therapy.

Dose augmentation

Eight patients received 40 mg/kg dose after a minimum of 26 weeks on alglucosidase alfa. Of these, five qualified for dose increase because of failure to demonstrate a clinically meaningful change from baseline in the Functional Skills Mobility domain score of the Pompe PEDI; four patients qualified because they required new respiratory support or had a clinically meaningful increase in the amount of required respiratory support (two of these also qualified based on motor function); and one patient qualified because of the development of clinical symptoms of cardiac failure. Clinical status for these patients remained largely unchanged after the dose increase; one patient resolved symptoms of cardiac failure but subsequently died of respiratory failure.

Safety results

Adverse events/infusion-associated events

Eleven (52%) patients experienced 42 IARs, which were defined as AEs occurring on the day of infusion and assessed by the investigator as being related to treatment. The most common IARs were skin and subcutaneous skin disorders (13 events); vascular disorders (10 events); and oxygen saturation, blood pressure increase, heart rate increase or respiratory rate increase (seven events). Flushing occurred in four patients, oxygen desaturation in three patients, and urticaria, pyrexia, cough, and tachypnea were observed in two patients each. Reactions were managed by slowing the infusion rate or temporarily stopping

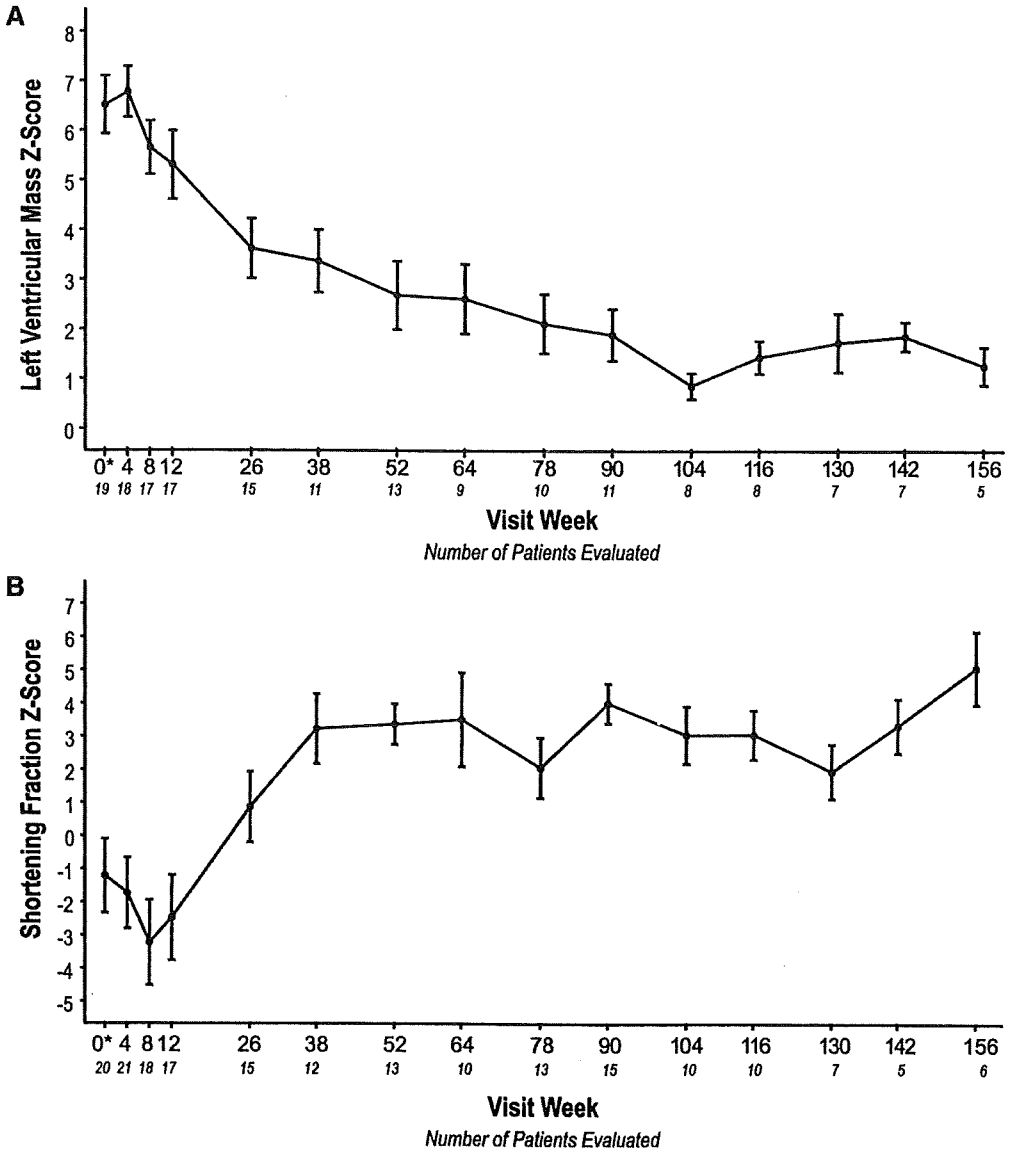

Fig. 1. (A) Mean LVM *Z* scores and (B) mean shortening fraction *Z* scores from baseline to last assessment; vertical bars indicate standard error. Dotted line represents a normal *Z* score.

the infusion and administering symptomatic treatment. All 11 patients recovered without sequelae and continued treatment. Retrospective analysis of two patients with IARs suggestive of hypersensitivity reactions found those patients to be IgE negative. Infusion interruption and symptomatic treatment resolved these reactions and both patients were rechallenged successfully.

Six patients died during the treatment period; none of the deaths were attributed to treatment. All of the deaths were attributed to cardiac and/or respiratory causes, including cardiac or cardiorespiratory arrest, acute pulmonary edema, arrhythmia, and respiratory failure secondary to bronchiolitis.

Antibody response

Nineteen of 20 (95%) patients with postbaseline blood draws developed IgG antibodies to alglucosidase alfa. All but one of these patients seroconverted by Week 12; the median time to seroconversion was 4 weeks. The one patient who remained seronegative died before Week 8. Of the 19 patients who seroconverted, two tested negative for IgG antibodies at their last assessment (at Weeks 104 and 156); the maximum titer reported for both of these patients was 400. At last assessment, 14 patients had antibody titers between 200 and 6400, whereas three patients had titers between 51,200 and 102,400. Of note, last IgG antibody titers in the two CRIM-patients were 102,400 (patient died in Week 15) and 6,400 (patient died in Week 101). None of the patients who seroconverted exhibited significant inhibitory antibody activity by either assay at any time point.

DISCUSSION

In this study, a group of infants and children with Pompe disease treated with alglucosidase alfa demonstrated improved survival and invasive ventilation-free survival in comparison

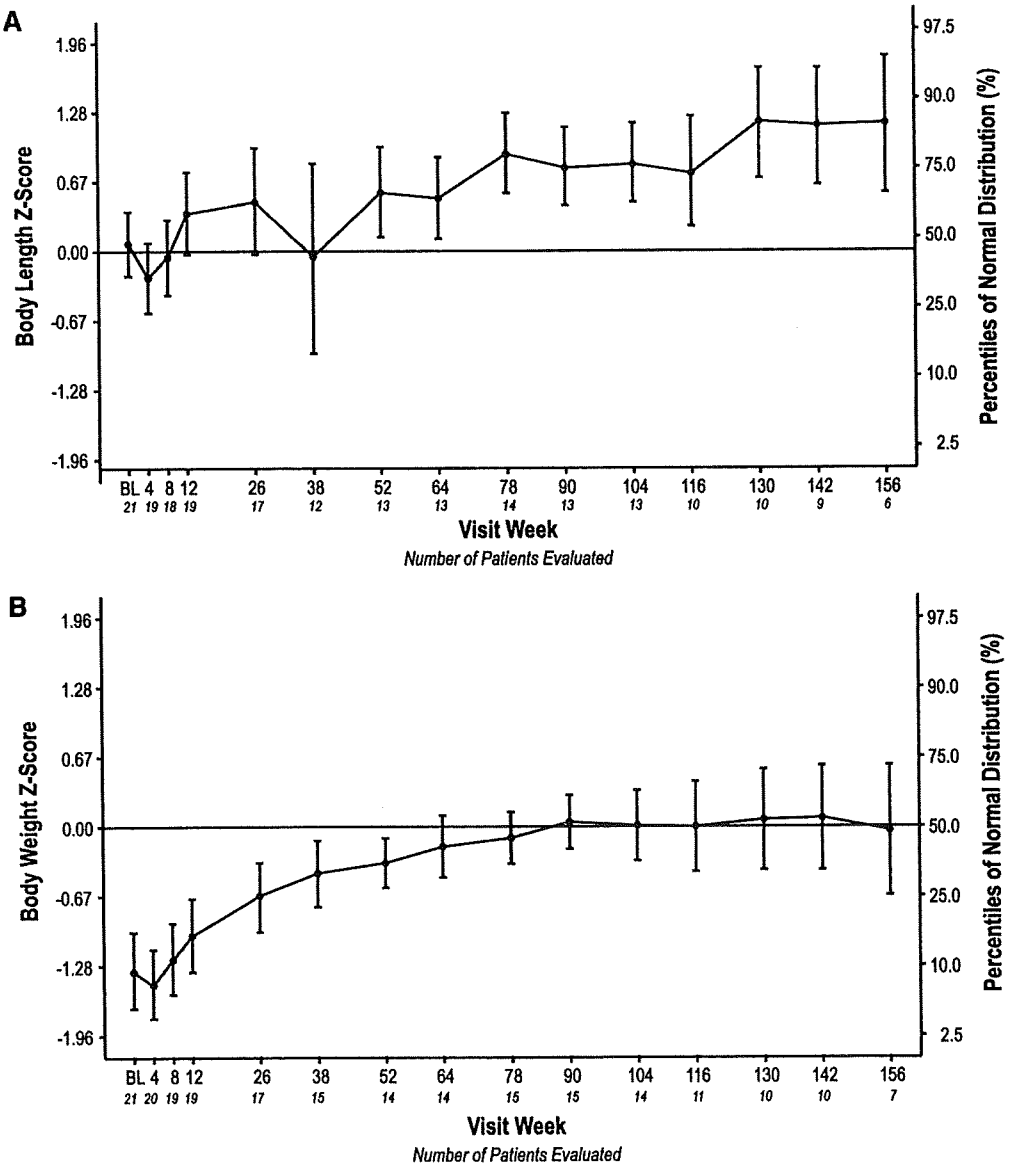

Fig. 2. (A) Mean body length *Z* scores and (B) mean body weight *Z* scores and relation to CDC growth chart norms.

with patients in an untreated reference cohort. All but one patient had onset of symptoms in the first 12 months of life and all exhibited signs of advanced disease (e.g., need for ventilator support, markedly delayed motor development, and/or elevated LVMI). A previous study showed that alglucosidase alfa significantly extended survival and ventilator-free survival in a more homogeneous group of young infants who were treated at a relatively early stage of disease progression.[3] The present study shows that this benefit extends to older infants and children.

In addition to improving survival in young patients, alglucosidase alfa has also been shown to improve Pompe disease manifestations such as indices of cardiomyopathy, and to allow patients to continue motor development beyond the point at which it is arrested in untreated patients.[3,9] In the present study, clear improvements over baseline were demonstrated in these areas. Although these outcomes were not directly compared with the untreated cohort, they contrast sharply with the well-documented natural course of the disease in infants and young children.[10,20]

In any rapidly progressing disease, age is typically associated with worsening clinical status. In natural history studies of Pompe disease, patients presenting with symptoms in the first year of life have poor prognoses. The historical, rigid separation of Pompe disease into infantile-onset and late-onset has come into question recently as more is learned about the inconsistency of age at clinical presentation and progression of disease; age at onset of symptoms of disease does not always correspond with speed of progression or prognosis. The current cohort is a group of patients with rapid yet variable disease progression, as demonstrated by the heterogeneity of age and clinical involvement at initiation of treatment. We included only patients with onset of disease symptoms in infancy and, with one exception, measurable cardiac involvement. Although these are the generally accepted criteria for infantile-onset Pompe disease, it is clear that the rate of disease progression varied in this cohort. Previ-

ous studies indicate that where there is cardiac involvement and motor impairment, disease progression is generally rapid in the absence of treatment. In this study, response to treatment was generally more pronounced in patients with better preservation of cardiac, respiratory, or skeletal muscle function at baseline. It is notable that patients who were older at the time of first ERT infusion (and therefore likely had a more slowly progressive disease course) had a better response to treatment. Of the four oldest patients, two normalized their LVM *Z* scores and all four had measurable motor gains with treatment. However, despite their advanced age by the end of the study (3–6 years, with treatment duration between 12 and 37 months), only one of these patients could walk by the end of the study and two remained dependent on invasive ventilation. These results suggest that baseline clinical status is a better indicator of Pompe disease progression and potential response to treatment than age alone.

In untreated Pompe disease, cardiomyopathy parameters observed in infants worsen over time and eventually lead to congestive heart failure.[10,20] In this study, all patients with echocardiograms beyond 12 weeks demonstrated improvement or maintenance of normal LVMI; notably more than half of patients attained a normal LVM (*Z* score ≤ 2) by last assessment. Measurements of cardiac function also improved; the initial, transient drop in mean SF that was observed may be due to an initial remodeling phase potentially prompted by the rapid removal of glycogen from the cardiac walls. The overall improvement in cardiac status likely contributed to the prolonged survival rates observed in this study.

Motor development is often completely arrested in untreated infants and children with Pompe disease, or if motor milestones are achieved, they are subsequently lost.[10,20] In the present study, many patients acquired new motor and functional skills. The majority of patients who did not show motor gains had undetectable muscle GAA activity and more advanced disease at baseline, including lower age-equivalent motor scores. Additionally, almost all patients in the study demonstrated the acquisition of functional skills as measured by the Pompe PEDI; this measure provides a more sensitive and comprehensive assessment of the ability to perform skills required for many activities of daily living than motor evaluations alone.[15,16]

Failure to thrive is another typical finding in infants with untreated Pompe disease.[10,20] A natural history study found that, despite the frequent use of tube feeding (in 59.5% of patients), 53% of untreated Pompe patients failed to maintain normal growth in the first year of life.[10] In contrast, in the present study, almost all patients maintained weight- and length-for-age percentiles above the 3rd percentile through the study. It should be noted that patients who required long-term invasive ventilation at any point in the study received tube feedings.

BSID-2 age-equivalent scores indicated continued cognitive, language, and personal-social development for the majority of patients. Little is known about cognitive development in infants with Pompe disease because of the early mortality observed in untreated patients; the interpretation of the findings observed is complicated by the difficulties inherent in performing a standardized test administration to patients who have oral-motor and gross- and fine-motor deficits, as well as possible hearing loss,[21] which may significantly affect test performance.

Previously published data suggest that the extent of muscle damage may predict response to treatment with alglucosidase alfa.[9,22] The results of this study provide additional support for this observation. Four patients who died before Week 52 had negligible baseline muscle GAA activity levels. Motor function at baseline was also worse in these patients (four had age-equivalent baseline motor scores of 1 month or lower) and one was already invasively ventilated at baseline. The patients who were walking or sitting independently at the end of the study, in contrast, had higher muscle GAA activity and better baseline motor function at baseline than those who made no significant motor gains, suggesting greater preservation of muscle tissue.

Although alglucosidase alfa seems to have increased the activity of GAA in muscle in this study, GAA activity levels changes did not consistently correlate with muscle glycogen content. This result is consistent with previous findings that increased muscle GAA activity after ERT does not always correlate with clearing glycogen from muscle tissues or with motor improvements.[9,10] It is notable that samples in this and previous studies[9,10] were taken exclusively from quadriceps; glycogen content measurements may not be consistent across various muscle groups in a single patient. Animal model studies have shown that glycogen clearance after rhGAA administration decreased as glycogen load increased (as animals aged).[23] Different muscle fiber types with varying density of receptors and degrees of autophagy may exhibit differential clearance of glycogen in the presence of enhanced GAA activity.[23–25]

Although approximately half of the patients treated with alglucosidase alfa in this study experienced IARs, none of the IARs led to the cessation of treatment. Although most patients developed antibodies against alglucosidase alfa, the majority showed a trend toward decreasing titers over time and none had evidence of in vitro inhibitory activity. The higher (40 mg/kg) dose of alglucosidase alfa was generally well tolerated, but this dose did not seem to change patients' clinical response. However, assessments and analyses were not resynchronized after a patient changed doses, and therefore meaningful conclusions regarding the safety or efficacy of the higher dose cannot be drawn from this study.

CONCLUSION

In this heterogeneous population of infants and children with advanced Pompe disease, ERT with alglucosidase alfa beginning after 6 months of age extended survival and invasive ventilator-free survival compared with the untreated reference group. In addition, the majority of patients treated with alglucosidase alfa improved echocardiographic indices of cardiomyopathy and made growth and motor development gains not typically observed in untreated infants and children. The results of this study are promising in that they show that alglucosidase alfa can reduce the mortality caused by this rapidly progressive, life-threatening disorder even when treatment is started at a more advanced stage of disease.

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ELSEVIER

Myoclonic Epilepsy With Ragged-Red Fibers Without Increased Lactate Levels

Shigemi Kimura, MD, PhD, Shiro Ozasa, MD, Kyoko Nakamura, MD, Keiko Nomura, MD, and Hirofumi Kosuge, MD

Myoclonic epilepsy associated with ragged-red fibers is one of the mitochondrial encephalomyopathies. Pathogenic mitochondrial DNA mutations have been identified in the mitochondrial transfer RNA (tRNA)^{Lys} at positions 8344 and 8356. Characteristics of myoclonic epilepsy associated with ragged-red fibers include myoclonic epilepsy, generalized epilepsy, hearing loss, exercise intolerance, lactic acidosis, and ragged-red fibers. The elevated lactate level is one of the most important symptoms needed to make a diagnosis of mitochondrial encephalomyopathy. In the present case, however, myoclonic epilepsy was associated with ragged-red fibers but without increased lactate levels. Therefore, myoclonic epilepsy associated with ragged-red fibers should be suspected in a patient who has myoclonic epilepsy that is difficult to control with antiepileptic medications and who has other symptoms of mitochondrial disease, such as mental retardation, even if the patient's lactate level is normal.

Kimura S, Ozasa S, Nakamura K, Nomura K, Kosuge H. Myoclonic epilepsy with ragged-red fibers without increased lactate levels. Pediatr Neurol 2009;41:46-48.

Introduction

Mitochondrial encephalomyopathies are classified primarily as chronic progressive external ophthalmoplegia [1], mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (or MELAS syndrome) [2], and myoclonic epilepsy with ragged-red fibers (or MERRF syndrome) [3]. Myoclonic epilepsy with ragged-red fibers is a multisystem disorder characterized by myoclonus, generalized epilepsy, ataxia, hearing loss, exercise intolerance, lactic acidosis, and ragged red fibers visualized by Gomori trichrome stain in muscle biopsy. The fibers also react intensely with succinate dehydrogenase stain. Furthermore, both ragged red fibers and some non-ragged red fibers fail to stain with the histochemical reaction for cytochrome *c* oxidase [4]. Myoclonic epilepsy with ragged-red fibers biopsies also show strongly succinate dehydrogenase-positive blood vessels, which are uniformly cytochrome *c* oxidase-negative.

Approximately 80-90% of patients with myoclonic epilepsy with ragged-red fibers have A8344 G mutations in the mitochondrial DNA tRNA^{Lys} gene [5]. The disease is maternally inherited. The first laboratory test needed for patients in whom mitochondrial encephalomyopathies are suspected is the measurement of the serum levels of lactate and pyruvate. Increased levels of lactate and pyruvate are strongly suggestive of the presence of a mitochondrial encephalomyopathy [6].

Presented here is a case of myoclonic epilepsy with ragged-red fibers but without increased lactate levels. The diagnosis was more easily identified because the patient's mother, maternal aunt, and maternal grandmother had already been diagnosed with myoclonic epilepsy with ragged-red fibers. Thus, myoclonic epilepsy with ragged-red fibers should be suspected in any patient who has the symptoms of mitochondrial encephalomyopathy and of myoclonic epilepsy that is difficult to control with antiepileptic drugs, even if the patient's lactate level is normal.

Case Report

The patient is a 15-year-old boy (III-2) (Fig 1). His mother (II-2), maternal aunt (II-1), and maternal grandmother (I-2) were previously diagnosed with myoclonic epilepsy with ragged-red fibers (Fig 1); their cases were described in 1998 by Mita et al. [7]. For all three of these previously described

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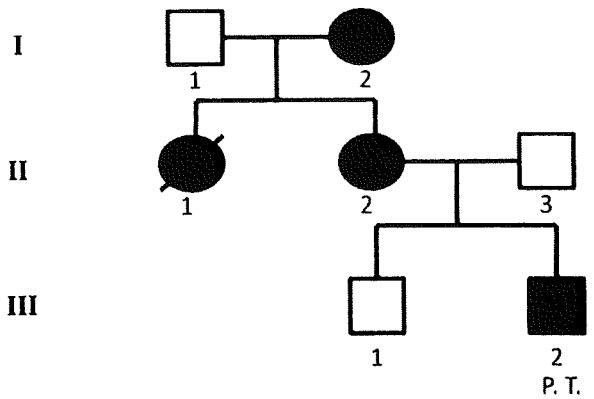

Figure 1. Pedigree of a family with myoclonic epilepsy with ragged-red fibers. The proband in the present case is individual III-2. Standard notation: solid symbols, affected; open symbols, unaffected; slash, deceased; square, male; circle, female.

patients, serum lactate and pyruvate levels were elevated. Individual II-2 evidenced only myoclonic epilepsy; individuals II-1 and I-2, however, had cerebellar ataxia and dilated cardiomyopathy, respectively, in addition to myoclonic epilepsy. All three had the A8344 G mutation in the mitochondrial DNA $tRNA^{Lys}$ gene, and their muscle biopsies showed ragged red fibers with Gomori trichrome stain.

The present patient (III-2) was referred because of epilepsy at the age of 7 years. Until then, he was developing normally; he had experienced two febrile convulsions as a 1-year-old. His intelligence quotient (IQ) score on the Wechsler Intelligence Scale for Children (3rd edition) was 89. During convulsions, which occurred when he was playing video games, his eyes were fixed and he became unconsciousness for approximately 1 minute. His electroencephalography showed paroxysmal polyspike and waves in diffuse distribution. His height was 119.3 cm (−0.1 standard deviation), and he weighed 21.1 kg (−0.3 standard deviation). He did not have excessive hair growth. Findings from cranial magnetic resonance imaging, chest X-ray, and electrocardiography were normal. He had normal levels of serum lactate (7.1 mg/dL; normal range, 4.0-14.2) and creatine kinase (145 U/L; normal range, 67-284). Thus, the results of these examinations did not indicate mitochondrial disease.

Nonetheless, because of his family history of myoclonic epilepsy with ragged-red fibers, informed consent was obtained and his mitochondrial DNA was examined. The mitochondrial DNA examination revealed the A8344 G mutation in the $tRNA^{Lys}$ gene in the lymphocytes, which is the same mutation found in his mother (II-2), aunt (II-1), and grandmother (I-2).

The patient's type of convulsions changed as he became older, developing variously into myoclonus and generalized tonic-clonic seizures with unconsciousness. The convulsions were very difficult to control with antiepileptic drugs; valproate, carbamazepine, nitrazepam, phenytoin, phenobarbital, and clonazepam were tried.

At the age of 14 years, the patient had mild mental retardation; his IQ score on the Wechsler Intelligence Scale for Children III was 73.

The patient's serum lactate level was checked at least four times per year from age 7 to age 15 years. The level had not increased over that time, not even after exercise. The lactate (13.6 mg/dL) and pyruvate levels (0.84 mg/dL) in cerebrospinal fluid were also normal at the age of 14 years. The patient did not have short stature at the age of 15 years.

Because the convulsions were difficult to control, a muscle biopsy was performed to aid in his diagnosis. Hematoxylin and eosin stain showed slight variations in myofiber size (Fig 2A). Gomori trichrome and nicotinamide adenine dinucleotide tetrazolium reductase stain showed ragged red fibers (Figs 2B and 2C). The muscle biopsy also revealed strongly succinate dehydrogenase-positive blood vessels (Fig 2D), cytochrome *c*

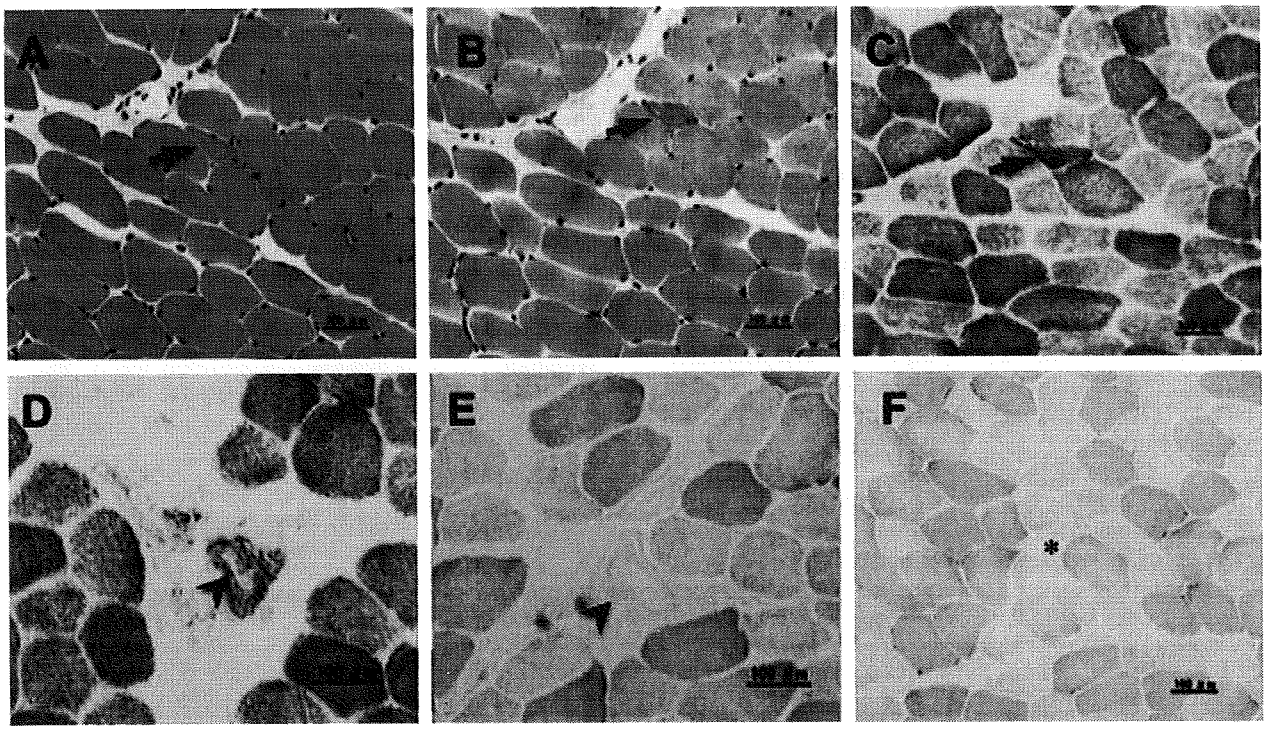

Figure 2. Cryostat sections from muscle biopsy of the proband. Note ragged-red fibers (arrows, A,B,C, serial sections), blood vessel strongly positive for succinate dehydrogenase (arrowhead, D), blood vessel negative for cytochrome c oxidase (arrowhead, E), and tissue uniformly negative for cytochrome c oxidase (asterisk, F). Stain: Hematoxylin and eosin (A), modified Gomori trichrome (B), nicotinamide adenine dinucleotide tetrazolium reductase (C), succinate dehydrogenase (D), and cytochrome c oxidase (E,F). Scale bar: 100 μm.

oxidase-negative vessels (Fig 2E), and uniformly cytochrome *c* oxidase-negative fibers (Fig 2F). These findings led to a conclusive diagnosis of myoclonic epilepsy with ragged-red fibers.

Discussion

Reported here is a case of myoclonic epilepsy with ragged-red fibers but without increased lactate levels. Lactate is ordinarily the most important marker in the diagnostic investigations for mitochondrial encephalomyopathies [6]. When mitochondrial disease is suspected, determination of the patient's lactate level is among the first evaluations performed. If the lactate level is normal, mitochondrial disease is excluded in the differential diagnosis. In the present case, however, the patient's lactate level has never been increased in either the serum or the cerebrospinal fluid. His only symptoms of mitochondrial disease are myoclonic epilepsy and mental retardation. It is hard to explain why the lactate level is not increased in this patient, and additional follow-up examinations are desirable.

A case of myoclonic epilepsy with ragged-red fibers without increased lactate levels in the serum and cerebrospinal fluid is a novel finding [8-10]. Nonetheless, a diagnosis of myoclonic epilepsy with ragged-red fibers was reasonably suspected, because the patient's mother, maternal aunt, and maternal grandmother had already been so diagnosed. Given the family history, even in the absence of increased lactate levels, the patient was diagnosed with myoclonic epilepsy with ragged-red fibers based on the results of a muscle biopsy that showed ragged-red fibers.

Myoclonic epilepsy with ragged-red fibers is one of the progressive myoclonic epilepsies, which are characterized by myoclonic seizures, tonic seizures, and progressive neurologic deterioration, typically with cerebellar signs and dementia [11]. Progressive myoclonic epilepsies are rare disorders and include Unverricht-Lundborg syndrome, neuronal ceroid lipofuscinosis, dentatorubral–pallidoluysian atrophy, and Lafora disease [11], in addition to myoclonic epilepsy with ragged-red fibers. Some cases of these diseases are difficult to diagnose. However, myoclonic epilepsy with ragged-red fibers is generally easy to diagnose among the progressive myoclonic epilepsies, because the lactate levels of patients with myoclonic epilepsy with ragged-red fibers progressive myoclonic epilepsies are high. The present case indicates that rule to be less than absolute. A patient with myoclonic epilepsy that is difficult to control with antiepileptic medications and whose IQ score is lower than a previous score should be suspected of having have myoclonic epilepsy with ragged-red fibers, even if the patient's lactate level is not increased [12].

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特集
臨床開発の最近の動向
臨床精神薬理　13：255-263, 2010

本邦における国際共同治験の現状と課題

——抗うつ薬開発の最近の動向——

中林哲夫*　中村治雅*,**　岡本長久***

抄録：治療環境の向上のためには，臨床での治療戦略の確立と並び，新規治療薬の開発も重要である。近年の精神神経疾患領域における欧米での新薬開発は活発である。本邦ではドラッグ・ラグは社会問題となっているが，海外と同時開発を行う方法の1つとして国際共同治験が提唱され，その実施数も増加しており，医薬品開発の方法として定着しつつある。本稿では，欧米では標準治療薬とは異なり新たな作用機序を有する化合物の臨床開発に突入しているうつ病領域に焦点を当て，新規治療薬の開発状況，臨床試験の実施状況，そして症例集積性について調査することで，本邦における国際共同治験の現状と課題について検討したので報告する。　臨床精神薬理　13：255-263, 2010

Key words：*multi-regional clinical trial, major depressive disorder, antidepressant, drug development delay, sample size*

はじめに

世界保健機関（WHO：World Health Organization）による世界疾病負荷調査（GBD：The Global Burden of Disease Study）[17]では，精神神経疾患の調整障害生存年数（DALYs：disability-adjusted life years）は疾患領域別で最も高く，重要な疾患領域と位置付けられている。また海外における精神神経疾患を対象とした臨床試験の登録件数は悪性疾患領域に次いで2位であり，なかでも大うつ病性障害（major depressive disorder，以下，うつ病）と統合失調症の登録件数が多く[7]，当該領域の新薬開発は活発である。

ドラッグ・ラグ（欧米で承認されている医薬品が本邦においては未承認であり，国民に提供されていない状態）は社会問題となっているが，海外と同時開発を行う方法の1つとして国際共同治験が提唱[13]され，既にその具体的方法についても規制当局により取りまとめられている[9]。本邦における国際共同治験の実施数は増加[6]しており，医薬品開発の方法として定着しつつある。

治療環境の向上のためには，臨床での治療戦略の確立と並び，新規治療薬の開発も重要である。本稿では，精神神経疾患の中でもうつ病に焦点を当て，新規治療薬の開発状況，臨床試験の実施状況，そして症例集積性（1施設当たりの平均実施症例数）について調査することで，本邦における国際共同治験の現状と課題について検討した。

Ⅰ．方　法

うつ病を対象とした未承認化合物（以下，うつ

Trends in drug development for major depressive disorder; multi-regional clinical trial.

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病対象化合物）の臨床開発の状況，臨床試験の実施状況，そして症例集積性について調査した。

うつ病対象化合物（表1，表2）の調査対象は，国内外で未承認でありphase Ⅱ以降の臨床試験が実施されている化合物とした。そして臨床試験の実施状況（表3，図1，図2）の調査対象は，2004年以降に企業主導で実施されたうつ病対象の臨床試験であり，国内外で既承認の抗うつ薬も含まれる。また，これらのうつ病対象化合物の開発状況および臨床試験の実施状況の調査では，双極性障害のみを対象とした化合物や臨床試験は含まない。症例集積性（表4）の調査対象は，2004年以降に本邦で承認された抗うつ薬であるsertraline hydrochloride（以下，sertraline）およびmirtazapineとした。

調査方法は，うつ病対象化合物および臨床試験の実施状況については，米国国立衛生研究所（National Institutes of Health，以下，NIH）の臨床試験登録データベース（http://www.clinicaltrials.gov/）を使用して，各化合物（表1，表2）の作用機序と開発状況については，新薬の研究開発データベース「明日の新薬」（https://asushin2.com/）を使用して調査した。調査の対象国は限定しなかったが，地域別の実施状況の比較（図2）では，試験計画と新薬承認審査の質的類似性をある程度担保するために，ICH（International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use）の主要3極である日本，米国そして欧州連合（European Union，以下，EU）と，この他に近隣のアジア諸国の状況も比較するために，2004年以降に臨床試験を実施している韓国，台湾，中国，フィリピン，香港およびシンガポールの6ヵ国も対象とした。症例集積性については，医薬品医療機器総合機構（PMDA：Pharmaceuticals and Medical Devices Agency）のホームページ（http://www.info.pmda.go.jp/shinyaku/shinyaku_index.html）で公開されている申請資料概要をもとに調査した。米国での承認年月（表4）については，FDA（U.S.Food and Drug Administration）のホームページ（http://www.fda.gov/）により調査を行った。いずれの調査も2009年9月30日時点の登録情報をもとに調査した。

Ⅱ．結　果

1．うつ病対象化合物の開発状況について

開発最高フェーズがphaseⅡおよびphaseⅢのうつ病対象化合物の開発状況は，既承認抗うつ薬の作用機序の類似性を考慮して，phaseⅢそしてphaseⅡの順で調査結果を提示する。

開発最高フェーズがphaseⅢにあるうつ病対象化合物の開発状況を表1に示した。phaseⅢの開発段階にある化合物は5品目存在した。そのうち4品目（LY-2216684，LU-AA21004，vilazodone hydrochloride，amibegron hydrochloride）がモノアミン類関連の化合物であり，そして3品目（LU-AA21004，vilazodone hydrochloride，amibegron hydrochloride）の機序は，SSRI（Selective Serotonin Reuptake Inhibitors）やSNRI（Serotonin and Norepinephrine Reuptake Inhibitors）にあるような再取り込み阻害ではなく，受容体に直接作用する化合物であった。また，モノアミン類関連以外の化合物としてglucocorticoid receptor antagonistであるORG-34517が存在した。phaseⅢにある化合物5品目の臨床試験には，米国は全品目（100.0%）に，EUは4品目（80.0%）に参加していたが，本邦で臨床開発段階にあるものは1品目（20.0%）のみであった。

開発最高フェーズがphaseⅡにあるうつ病対象化合物の開発状況を表2に示した。phaseⅡの開発段階にある化合物は24品目存在した。phaseⅢにはなくphaseⅡにある作用機序の化合物として，TRI（triple reuptake inhibitor，serotonin-noradrenaline-dopamine reuptake inhibitor）があるが，これはSSRIおよびSNRIと異なりdopamineに対しても再取り込み阻害作用を有する化合物であった。またこの他に新たな作用機序を有する化合物として，神経ペプチド類関連のNK（neurokinin）1 antagonist，CRF（corticotropin-releasing factor）1 antagonist，vasopressin V1b antagonistが存在し，グルタミン酸関連のNMDA（N-methyl-D-aspartic acid）antagonistやAMPA

表1　Phase Ⅲにあるうつ病対象化合物の開発状況（2009年9月30日時点）

分類	化合物名	作用機序[a]	開発会社	臨床試験実施状況		
				米国	EU	日本
臨床試験参加率（%）[b]				100.0(5/5)	80.0(4/5)	20.0(1/5)
モノアミン類関連	LY-2216684	NRI	Eli Lilly	Phase Ⅲ	Phase Ⅲ	—
	LU-AA21004	serotonin 3 antagonist, serotonin 1A partial agonist	武田薬品工業, Lundbeck	Phase Ⅲ	Phase Ⅲ	Phase Ⅰ
	vilazodone hydrochloride	serotonin uptake inhibitor, serotonin 1 A partial agonist	Clinical Data, Merck KGaA	Phase Ⅲ	Phase Ⅱ（中止）	—
	amibegron hydrochloride	β 3 agonist	sanofi-aventis	Phase Ⅲ	Phase Ⅲ	—
その他	ORG-34517	glucocorticoid receptor antagonist	Schering-Plough	Phase Ⅲ	—	—

a)「明日の新薬」（https://asushin2.com/）を使用した調査結果。
NRI：selective noradrenaline reuptake inhibitor
b) 臨床試験参加率（%）＝各国で臨床試験が実施されている品目数/最高フェーズがphaseⅢの全うつ病対象化合物数（5品目）

(α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid) agonistが存在した。phaseⅡにある化合物の作用機序の種類は，phaseⅢにある化合物と比較して多様であった。phaseⅡにある化合物24品目の臨床試験のうち，米国は20品目（83.3%）に，EUは11品目（45.8%）に参加し，米国と比較してEUの参加率は低く，本邦からの参加は2品目（8.3%）のみであった。

2．臨床試験の実施状況について

2004年以降に企業主導でphaseⅡおよびphaseⅢとして実施されたうつ病対象の臨床試験の国別試験数と国際共同による試験（multi-regional clinical trial，以下，MRCT）が占める割合を図1に示した。図1では，国内外で既承認の抗うつ薬も含み，総試験数が3以上の国について表示した。総試験数では，米国（92試験），カナダ（28試験），ロシア（23試験），フランス（20試験）そしてドイツおよびフィンランド（各19試験）が上位6ヵ国であった。本邦の試験数（11試験）は，近隣アジア6ヵ国（韓国：10試験，台湾：9試験，中国およびフィリピン：各5試験，香港：3試験，シンガポール：1試験）と比較して多かったが，その差は大きなものではなかった。各国のMRCTが占める割合は，EU各国と比較して米国（35/92試験，38.0%）で低かったが，本邦（1/11試験，9.1%）ではさらに低かった。

2004年以降に企業主導でphaseⅡおよびphaseⅢとして実施されたうつ病対象の臨床試験の地域別および開発phase別の試験数を図2に示した。図2でも国内外で既承認の抗うつ薬も含み，phaseⅠ/ⅡはphaseⅡとして，phaseⅡ/ⅢはphaseⅢとして扱い，MRCTと各国内のみで実施している試験（non-MRCT）別に図示した。また，EUについても単独の国のみで行われている臨床試験をnon-MRCTとして扱った。総試験数は，米国で92試験（phaseⅡ：29試験，phaseⅢ：63試験），EUで45試験（phaseⅡ：15試験，phaseⅢ：30試験）であり，米国の方が多かった。EUとアジア諸国（韓国，台湾，中国，フィリピン，香港およびシンガポール）は大部分がMRCT（EU：93.3%，アジア諸国：86.7%）であった。アジア諸国では，臨床試験の大部分がphaseⅢ（93.3%）であり，phaseⅡとして参加してい

表2　Phase Ⅱにあるうつ病対象化合物の開発状況（2009年9月30日時点）

分類	化合物名	作用機序[a]	開発会社	臨床試験実施状況		
				米国	EU	日本
臨床試験参加率（%）[b]				83.3(20/24)	45.8(11/24)	8.3(2/24)
モノアミン類関連	SEP-225289	TRI	Sepracor	Phase Ⅱ	—	—
	DOV-216303	TRI	Dov Pharmaceutical	Phase Ⅱ	Phase Ⅱ	—
	LU-AA24530	Mixed serotonin modulator	武田薬品工業, Lundbeck	—	Phase Ⅱ	Phase Ⅰ
	GSK-163090	serotonin 1 antagonist	GlaxoSmithKline	Phase Ⅰ	Phase Ⅰ	—
	levomilnacipran hydrochloride	SNRI	Pierre Fabre, Forest Laboratories	—	Phase Ⅱ	—
	CX-157	MAO A inhibitor	CeNeRx BioPharma	Phase Ⅱ	—	—
タキキニン類関連	orvepitant maleate	NK 1 antagonist	GlaxoSmithKline	Phase Ⅱ	Phase Ⅰ	—
	vestipitant mesilate	NK 1 antagonist	GlaxoSmithKline	Phase Ⅱ	Phase Ⅱ	—
	CP-122721	NK 1 antagonist	Pfizer	Phase Ⅱ	—	—
CRF 関連	verucerfont	CRF 1 antagonist	GlaxoSmithKline	Phase Ⅱ	Phase Ⅰ	—
	emicerfont	CRF 1 antagonist	GlaxoSmithKline	Phase Ⅰ	—	—
vasopressin 関連	nelivaptan	vasopressin V 1 b antagonist	sanofi-aventis	Phase Ⅱ	Phase Ⅱ	—
グルタミン酸関連	AZD-6765	NMDA antagonist	AstraZeneca	Phase Ⅱ	—	Phase Ⅰ
	farampator	AMPA agonist	Cortex Pharmaceuticals, Schering-Plough	Phase Ⅱ	—	—
	ORG-26576	AMPA agonist	Schering-Plough	Phase Ⅱ	—	—
コリン類関連	coluracetam	choline uptake enhancer	BrainCells	Phase Ⅱ	—	—
その他	SSR-411298	FAAH inhibitor	sanofi-aventis	—	Phase Ⅱ	—
	SA-4503	opioid σ 1 receptor agonist	M's Science	Phase Ⅱ	Phase Ⅱ	—
	losmapimod	p38 kinase inhibitor	GlaxoSmithKline	Phase Ⅱ	—	—
	AZD-2327	enkephalin receptor modulator	AstraZeneca	Phase Ⅱ	—	—
不明	ADX-N05	—	Addrenex Pharmaceuticals	Phase Ⅱ	—	—
	ORG-34167	—	Schering-Plough	—	Phase Ⅱ	—
	RO-4917523	—	Roche	Phase Ⅱ	—	—
	R-228060	—	Janssen Pharmaceutica	Phase Ⅱ	—	—

a)「明日の新薬」(https://asushin2.com/) を使用した調査結果。
SNRI：serotonin-noradrenaline reuptake inhibitor, TRI：triple reuptake inhibitor（serotonin-noradrenaline-dopamine reuptake inhibitor), NK 1 ：neurokinin 1 , CRF：corticotrophin-releasing factor, FAAH：fatty acid amide hydrolase, NMDA：N-methyl-D-aspartic acid, AMPA：α-amino-3-hydroxy-5-methyl-4-isoxazole-propionate

b) 臨床試験参加率(%) = 各国で臨床試験が実施されている品目数/最高フェーズがphase Ⅱの全うつ病対象化合物数（24品目）

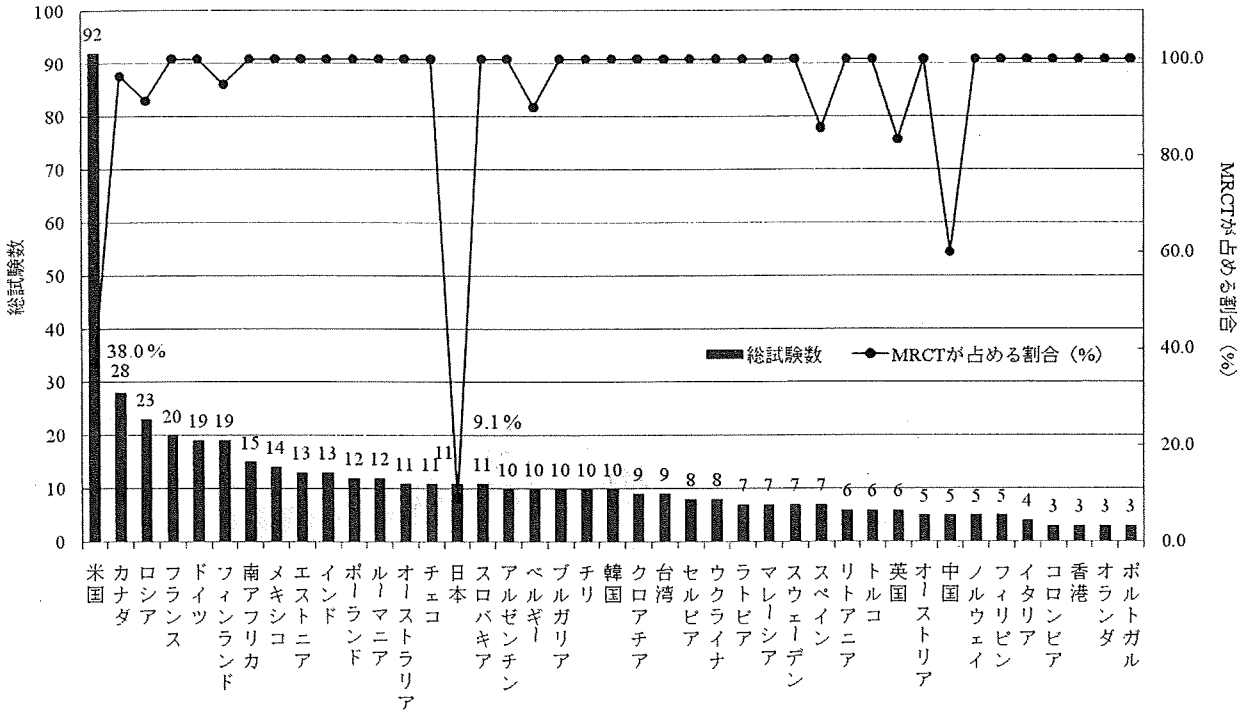


図1　2004年以降に企業主導で実施されたうつ病対象の臨床試験の国別試験数と国際共同試験（MRCT）が占める割合（phaseⅡおよびphaseⅢ，総試験数が3以上の国を表示）

るのは，MRCTの1試験のみであった。本邦でうつ病を対象に実施されているMRCTは1試験のみで，Desvenlafaxine Succinateのphase Ⅲ試験であり，当該化合物のphase Ⅱ試験は本邦では行われていない。

2004年以降に本邦およびアジア各国において企業主導で実施されたうつ病対象の臨床試験数を開始年別に表3に示し，2009年については9月30日時点の調査であるため，2008年と2009年を併合して表示した。韓国，台湾およびマレーシアの3国では，2007年以降に開始された臨床試験数が増加する傾向が認められた。

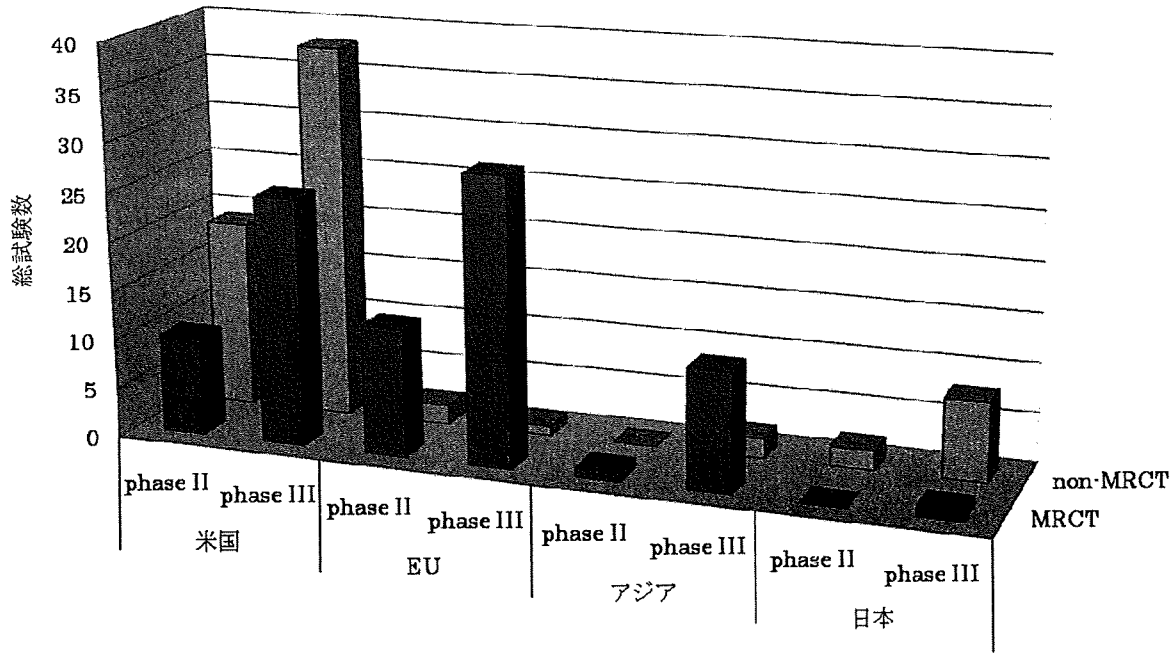
3．抗うつ薬の臨床試験の症例集積性について

Sertralineおよびmirtazapineについて，本邦での承認申請で提出された臨床試験における症例集積性を表4に示した。海外試験については，プラセボ群が設定された無作為化二重盲検並行群間比較法で実施された試験のうち，第Ⅳ相試験を除外したものを表示した。各薬剤の承認時期は，sertralineは本邦が2006年4月，米国が1991年12月で，mirtazapineは本邦が2009年7月，米国が1996年6月であり，いずれも承認時期が大きく異なるが，表4にあげた全ての臨床試験の実施時期は公開されていない。Sertralineの臨床試験における症例集積性は，国内で3.3～6.6例/施設，海外で7.6～315.0例/施設であった。Mirtazapineの臨床試験における症例集積性は，国内で6.0～6.2例/施設，海外で14.6～150.0例/施設であった。Sertralineおよびmirtazapineの臨床試験とも，症例集積性は国内と比較して海外で高かった。

Ⅲ．考　察

1．現在開発中のうつ病対象化合物の作用機序における特徴について

本邦でのSSRI導入から10年が経過しようとしており，SSRI（paroxetine, fluvoxamine, sertraline），そしてSNRI（milnacipran）の使用経験は十分に蓄積できている。欧米で標準治療薬[1,2,5,15]として位置付けられている抗うつ薬のうちfluoxetine, citalopram, escitalopram, venlafaxine,



	米国		EU		アジア		日本	
	phase II	phase III	phase II	phase III	phase II	phase III	phase II	phase III
■MRCT	10	25	13	29	1	12	0	1
■non-MRCT	19	38	2	1	0	2	2	8

MRCT：国際共同の臨床試験，non-MRCT：各国単独による臨床試験
アジア：近隣6ヵ国（韓国，台湾，中国，フィリピン，香港，シンガポール）

図2　2004年以降に企業主導で実施されたうつ病対象の臨床試験数（地域別，開発相別）

duloxetine および bupropion は本邦で未承認であるが，mirtazapine も承認され，既に主要な抗うつ剤が本邦の臨床現場には届いている。現在の開発相が phase Ⅱ および phase Ⅲ にあるうつ病対象の化合物（表1，表2）からも，欧米での SSRI の開発は終了していることがわかる。

現在開発中のうつ病対象化合物（表1，表2）の特徴は既に報告しているが[14]，欧米では神経ペプチド類やグルタミン酸関連等のモノアミン仮説を超える化合物が既に臨床開発の段階にあり，開発は新しい世代に突入している。

一般に薬剤開発の成功確率は高いものではなく，中枢神経領域の化合物での臨床試験の成功確率は，phase Ⅱ および phase Ⅲ とも40～50％であり，初回の臨床試験からでは10％未満[8]であるが，成功確率が高くないことは抗うつ薬においても例外ではない。つまり，現在開発中の化合物（表1，表2）の全てが新薬として承認されるわけではないが，EU では，2009年2月に melatonin 1 / 2 agonist，serotonin 2 C antagonist である agomelatine が承認[4]されており，従来の抗うつ薬とは異なる作用機序を有する新薬の導入が既に具体化した。

2．本邦の抗うつ薬の開発における問題と課題について

今回の調査より，本邦における抗うつ薬の開発上の問題として以下の点があげられる。

・臨床開発の着手が欧米と比較して遅れていること
・国際共同治験への参加が海外と比較して極端に少ないこと
・phase Ⅱ の国際共同治験に参加できていないこと

表3　2004年以降に本邦とアジア各国において企業主導で実施されたうつ病対象の臨床試験数（開始年別）

	2004年	2005年	2006年	2007年	2008～2009年	合計
日本	3	0	2	0	6	11
韓国	0	0	1	4	5	10
台湾	0	1	0	3	5	9
マレーシア	0	0	1	2	4	7
中国	1	0	2	1	1	5
フィリピン	0	0	1	1	3	5
香港	0	1	0	0	2	3
シンガポール	0	1	0	0	0	1

国内外で未承認であり開発相がphaseⅡもしくはphaseⅢの段階にあるうつ病対象化合物の臨床試験に本邦の参加が不十分（表1，表2）であるということは，今後もドラッグ・ラグが持続する可能性がある。また，国際共同治験においては，phaseⅡの用量反応性を探索的に検討する段階の試験に本邦は参加できていない（図2）。新薬開発においては，海外の臨床試験成績のみでなく日本人での用量反応性を検討することは，有効性と安全性を評価する上で重要な過程[9,10,12]であり，これらの医薬品をより適切な形で速やかに本邦に導入するためには，欧米と並び早期の段階から参加することが重要である。このためには，本邦の臨床試験の質においても欧米と並び一定の評価が得られるような実施体制についても検討していくことが必要である。

本邦における臨床試験の実施上の課題を検討するために，今回は症例集積性について検討した。近年承認された抗うつ薬2剤（sertralineおよびmirtazapine）とも，国内試験と海外試験の実施時期は大きく異なり，単純に国内外の比較はできないことに留意する必要はある。最近の海外試験の症例集積性は変化している可能性もあるが，いずれにしてもICH E9ガイドライン[11]で，臨床試験の質的担保のためにも症例集積性を高める必要があることが説明されている通り，さらに高める方策を検討する必要がある。

国際共同治験における日本人症例数は，全集団での結果と日本人集団での結果に一貫性が得られるように計画[9]される。各国の計画症例数は設定されてはいるが，組入れは一般に競合的に行われ，計画症例数を大きく下回った場合には日本人集団の成績を評価することが困難となる可能性がある。近年は試験デザインの工夫もあり，アダプティブ・デザイン[11,16]も中枢神経領域の臨床試験に導入されているが，当該デザインが用いられた国際共同治験に参加し日本人集団の用量探索を行う場合には，組入れ速度は特に問題となる。組入れ速度は症例集積性とも交絡する可能性もあるため，今後は同時に検討することが必要である。

3．本調査の方法論的限界

本調査は，臨床試験の現在の実施状況を調査することができ，一般にアクセス可能なデータベースであるNIHの臨床試験登録データベースを主体に調査したが，方法論的限界として，全ての臨床試験が登録されていない可能性と最新の情報に更新されていない可能性が残る。また，当該データベースでは実施症例数が特定できないため，症例集積性については既承認薬剤の申請資料概要を使用したが，国内外の臨床試験の実施時期は大きく異なるため，最近の海外の症例集積性についてはさらに検討が必要である。

表4　Sertraline および mirtazapine の臨床試験における症例集積性

一般名	実施国[a]		開発相[b]	試験名(試験番号)[c]	実施症例数	試験施設数	症例集積性[d]
sertraline hydrochloride 米国承認：1991年12月 本邦承認：2006年4月	国内		Ⅱ	STL-JP-92-001	60	15	4.0
			Ⅱ	STL-JP-92-002	92	27	3.4
			Ⅱ	STL-JP-93-602	142	41	3.5
			Ⅲ	STL-JP-94-607	174	53	3.3
			Ⅲ	STL-JP-94-608	196	45	4.4
			－	A0501048	361	55	6.6
	海外	米国	－	050-013	369	8	46.1
		米国	－	86CE21-0238	199	5	39.8
		フランス	－	050-334	258	34	7.6
		米国	－	050-104	448	8	56.0
		米国	－	050-109	315	1	315.0
		米国	－	R-0617	392	15	26.1
		英国	－	050-315	242	15	16.1
		フランス	－	050-320	467	39	12.0
mirtazapine 米国承認：1996年6月 本邦承認：2009年7月	国内		Ⅱ	001	281	45	6.2
			Ⅲ	9902	203	34	6.0
	海外	米国	Ⅱ	003-002	45	1	45.0
		米国		003-003	45	1	45.0
		英国		050	51	1	51.0
		米国		003-020	130	1	130.0
		米国		003-021	150	1	150.0
		米国		003-022	150	1	150.0
		米国	Ⅲ	003-008	150	2	75.0
		米国		003-042	281	5	56.2
		フィンランド		023	117	8	14.6
		英国		027	132	3	44.0
		米国		003-041	421	12	35.1
		米国		003-023	150	1	150.0
		米国		003-024	150	1	150.0

a) 海外試験は，プラセボ群が設定された無作為化二重盲検並行群間比較法で実施された試験のうち第Ⅳ相試験を除外した
b) 開発相が公開されていないものは「－」で表示した
c) 公開されている試験名を表示
d) 症例集積性：1施設当たりの実施症例数（＝実施症例数/試験施設数）

Ⅳ. 結　語

本邦における国際共同治験の現状と課題を検討するために，うつ病を対象とした化合物の開発状況，臨床試験の実施状況，そして症例集積性について検討した。今回の調査では，開発については，臨床開発の着手が欧米と比較して遅れていること，国際共同治験の参加がまだ少なくphase Ⅱへの参加が行えていないことが確認された。また，臨床試験自体については，国内の症例集積性が低く臨床現場にも課題があることが確認された。アジア諸国において急激に開発が活発化する中，リーダーシップを保ち続けられるよう，本邦における臨床試験の基盤については今後も更なる整備が必要であると考える。

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