An Overview of the Clinical Characteristics of Japanese Patients with Spinal Muscular Atrophy: Data from SMART Consortium

TWMUJ 5: 93-102, 2021

Original

An Overview of the Clinical Characteristics of Japanese Patients with Spinal Muscular Atrophy: Data from SMART Consortium

Tamaki Kato, Mari Urano, Mari Matsuo, and **Kayoko Saito**

Institute of Medical Genetics, Tokyo Women's Medical University, Tokyo, Japan

(Accepted August 11, 2021)
(Advance Publication by J-STAGE November 2, 2021)

Background: Patient registries play an important role in rare disease, particularly for recruitment of clinical trials and clinical research.

Methods: In 2012, we launched a registry for the purpose of clarifying the clinical characteristics of spinal muscular atrophy (SMA) in Japan and with the goal of enrolling patients with SMA into newly started clinical trials. In order to document the current status of SMA in Japan, we conducted a survey based on the data of 277 SMA patients enrolled in the registry from October 2012 to July 2020.

Results: Genetic testing was performed in 95% of patients. Patients with type III SMA experienced the longest onset to genetic diagnosis times, while those with type I had the shortest times. Tongue fasciculation was more common in types I and II SMA, while finger fasciculation was more common in types II and III. The site of fasciculation was thought to be the key to predicting the disease type. Over-the-counter or investigational drugs were administered to 76% of patients as of June 2019.

Conclusion: Our registry is useful for understanding the current status of SMA patients in Japan, and can provide accurate and up-to-date information on the clinical course of patients over their lifetime.

Keywords: national registry, spinal muscular atrophy, clinical characteristics, Japan

Introduction

Spinal muscular atrophy (SMA) is an autosomal recessive disorder characterized by degeneration of motor neurons in the anterior horn cells of the spinal cord.[1] SMA has been categorized into four types according to the time of onset and severity of the disease, and we have previously divided SMA into subtypes (Ia, Ib, IIa, IIb, IIIa and IIIb) based on changes in individual motor milestones.[2]

There are internationally integrated registries (TREAT-NMD,[3] Cure SMA,[4-6] SMARTCARE,[7] and iSMAC[8]), and RESTORE,[9] which is operated by a pharmaceutical company (**Table S1**). In 2012, we developed a registry of Japanese patients with SMA (Spinal Muscular Atrophy Research and Treatment consortium ; SMART consortium. https://www.sma-rt.org/) to collect information regarding the most up-to-date treatments and to promote clinical trials and the development of novel treatments for SMA. Through SMART consortium, we

Corresponding Author: Kayoko Saito, Institute of Medical Genetics, Tokyo Women's Medical University, 8-1 Kawada-cho, Shinjuku-ku, Tokyo 162-8666, Japan. saito.kayoko@twmu.ac.jp

doi: 10.24488/twmuj.2021010

have promoted enrollment in therapeutic research.

The therapeutic strategies for SMA aim to increase the survival of motor neuron (SMN) protein levels in motor neurons.[10] Valproic acid is a histone deacetylase inhibitor that increases SMN mRNA and protein expression; however, not all patients respond to it.[11] The first successful therapeutic approach involved the delivery of nusinersen (Ionis Pharmaceuticals/Biogen), an antisense oligonucleotide that was developed to inhibit exon 7 splicing in *SMN2,* to the central nervous system by intrathecal administration;[12-14] this treatment was approved in July 2017 in Japan. The one-time administration of intravenous gene therapy using onasemnogene abeparvovec, which produces SMN protein, is another successful approach;[15, 16] this treatment was approved in March 2020 in Japan. In addition, small molecule drugs, such as risdiplam, are awaiting approval in Japan.[17, 18] Until recently, patients with SMA only received symptomatic therapy or physiotherapy. However, nusinersen has been a breakthrough drug that has led to the further development of new therapeutics for SMA.

With the advent of SMA treatment, for which there has been no cure until now, up-to-date information on the current status of SMA patients is needed. Therefore, in this report we document the current status of SMA in Japan.

Materials and Methods

1. SMART consortium

The SMART consortium is a database of clinically diagnosed Japanese patients with SMA. Information about this registry was provided to interested individuals, and informed consent was obtained from the patient or their parents. It was stipulated that none of the data would be shared with any third party without the permission of the committee responsible for disclosing the information. Inclusion in the database confers no obligation on the patient, and removal from the registry is carried out immediately upon request. It was stated that the refusal to participate would not affect the subsequent medical care of the patient. The current status of the registry is shown in **Figure 1**. This study was approved by the Institutional Review Board of Tokyo Women's Medical University (Shinjuku, Tokyo, Japan).

2. Data from SMART consortium

Data obtained from the registry included the diagnosis, SMA type, family history, consanguinity, molecular genetic data, names of the medical institution that carried out genetic diagnosis and of the contract inspection company, presence/absence of fasciculation (and if present, appearance and site [tongue, fingers]), best reported motor function, current motor function, age of achievement of sitting/walking, age of loss of sitting/walking, wheelchair use, intellectual disability, intelligence quotient (IQ), cardiac dysfunction, respiratory dysfunction, requirement of artificial respiration, scoliosis, and history of scoliosis surgery.

3. Patient registration

Participants downloaded a registration form, an explanatory document, and a consent form. The doctors in charge of the SMART consortium homepage explained these documents to the patients. The participants filled out the registration form as completely as possible. During their next visit, the doctors completed the registration form and explanatory document, and gave the participants a copy of the results of their genetic test. The registration form, consent form, and a copy of the genetic test results were then mailed to the secretariat by registered mail. Finally, a registration certificate was sent by the secretariat (**Figure S1**).

4. Questionnaire on therapeutic drugs

We sent a questionnaire to the participants focused on the administration of post-marketing surveillance study and clinical trial therapeutic drugs to registered patients in June 2019, and subsequently collected their responses. Data about the drug types and effects were obtained. At the time the questionnaire was sent, only nusinersen was approved in Japan, valproic acid, risdiplam and onasemnogene abeparvovec were ongoing clinical trials. We evaluated the effects of these drugs on finger, arm, shoulder, and proximal and distal lower extremity movements as well as on improvements in fatigue and posture.

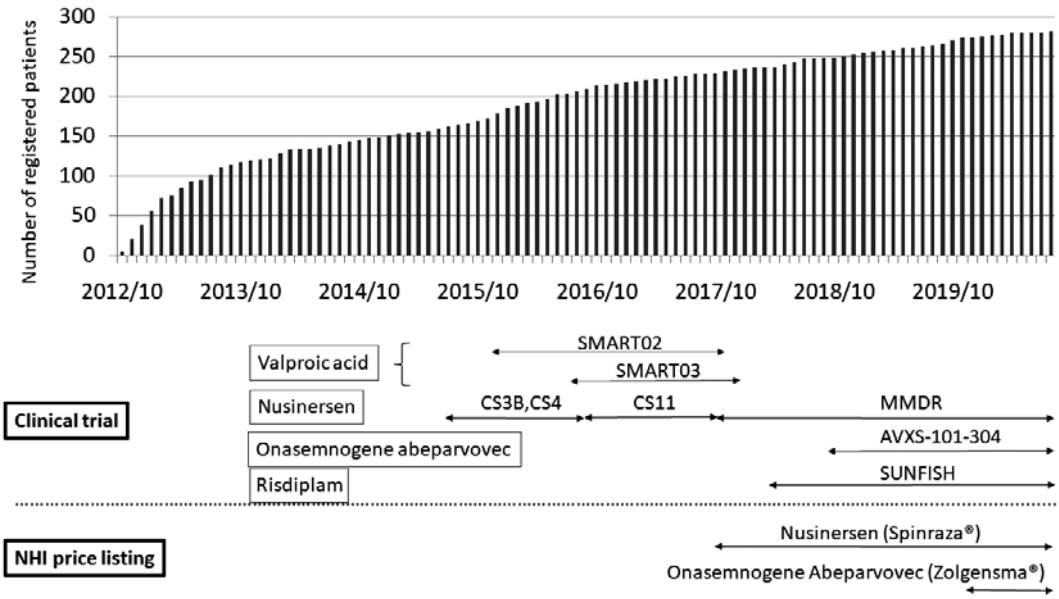


Figure 1. Changes in the number of patients enrolled in our registry and the duration of the clinical trials of SMA.
SMART02: Multicenter cooperative and investigator initiated clinical trial using valproic acid in childhood onset spinal muscular atrophy: Confirmatory Trial.
SMART03: Multicenter cooperative and investigator initiated clinical trial using valproic acid in childhood onset spinal muscular atrophy: Continuous administration trial.
CS3B: A Study to Assess the Efficacy and Safety of Nusinersen (ISIS 396443) in Infants With Spinal Muscular Atrophy (ENDEAR).
CS4: A Study to Assess the Efficacy and Safety of Nusinersen (ISIS 396443) in Participants With Later-onset Spinal Muscular Atrophy (SMA) (CHERISH).
CS11: A Study for Participants With Spinal Muscular Atrophy (SMA) Who Previously Participated in Nusinersen (ISIS 396443) Investigational Studies (SHINE).
MMDR: Modified maintenance dosing regimen.
AVXS-101-304: Pre-Symptomatic Study of Intravenous Onasemnogene Abeparvovec-xioi in Spinal Muscular Atrophy (SMA) for Patients With Multiple Copies of SMN2 (SPR1NT).
SUNFISH: A Study to Investigate the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics and Efficacy of Risdiplam (RO7034067) in Type 2 and 3 Spinal Muscular Atrophy (SMA) Participants (SUNFISH).

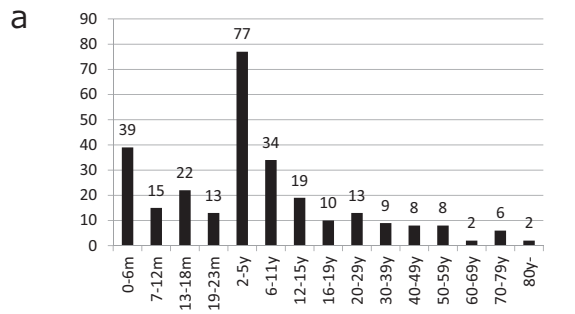
Results

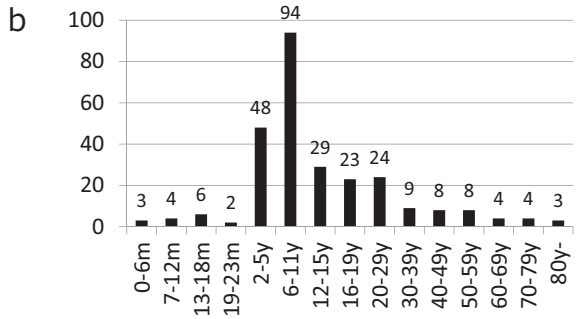
1. Demographics

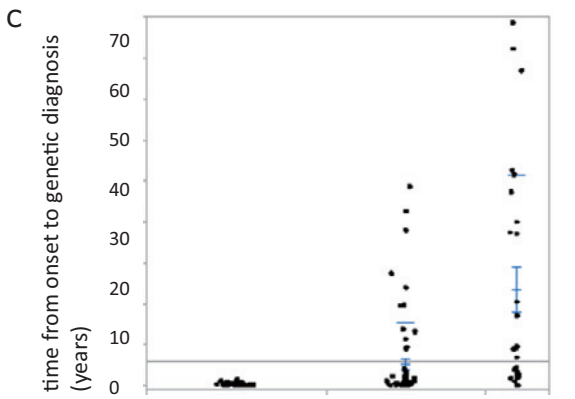
From October 2012 to July 2020, 277 Japanese patients with SMA (146 males and 131 females) were registered. SMA is diagnosed clinically by the attending physician, and some patients are also diagnosed genetically.[19, 20] Their representation according to subtype were as follows: type I, 40% (n=110); type II, 40% (n=111); type III, 15% (n=41); type IV, 4% (n=10); before the onset of symptoms, 1% (n=3); SMA with respiratory distress type 1, 0.4% (n=1); and suspected, 0.4% (n=1; **Table 1**).

Table 1. Patients profiles and clinical types.

	no. of patients
total	277
sex	
male	146
female	131
type	
I	110
II	111
III	41
IV	10
before the onset of symptoms	3
SMARD1	1
suspected	1







type	I	II	III
number	74	65	26
minimum(months)	0	2	8
maximum(years)	1.2	41	74
mean(years)	0.3	4.9	21
median(years)	0.3	0.8	7.6

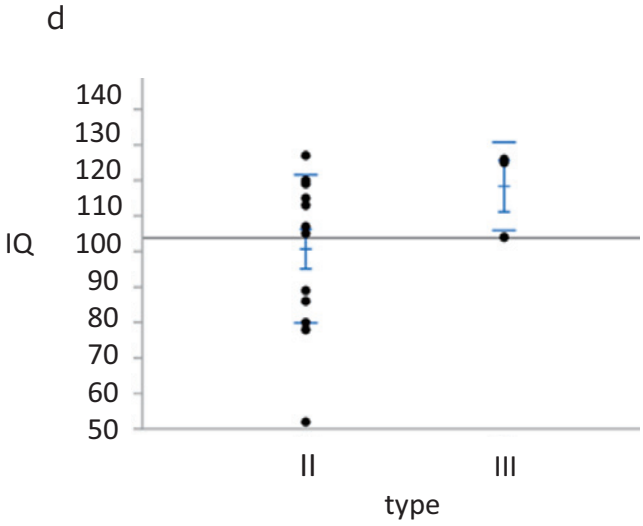


Figure 2. Epidemiology.
a (upper left). Age at registration.
b (upper right). Age as of July 2019.
c (lower left). Months from onset to genetic diagnosis.
Type I (n=74): median 3 months, mean 3.6 months, standard deviation 3.2 months.
Type II (n=65): median 9 months, mean 50.5 months, standard deviation 103.2 months.
Type III (n=26): median 91.5 months, mean 235 months, standard deviation 278.3 months.
d (lower right). Results of intelligence testing (IQ).

Most patients were 2-5 years old at the time of registration. The average age at the time of registration was 3.0, 9.9, 26.3, and 64.6 years for patients with types I, II, III, and IV SMA, respectively (**Figure 2a**). As of March 2020, surviving patients were typically aged 6-11 years, with an average age of 7.9, 15.6, 31.6, and 68.9 years for patients with types I, II, III, and IV SMA, respectively (**Figure 2b**).

The time from onset to genetic diagnosis was 0.3/0.3, 4.9/0.8, and 21/7.6 years (median/mean) for patients with type I (n=74), II (n=65), and III (n=26) SMA, respectively (**Figure 2c**).

Patients were registered from all over Japan, with Tokyo (n=34), Kanagawa (n=27), Fukuoka (n=19), Osaka (n=14), Aichi (n=11), Saitama (n=11), and Chiba (n=11) prefectures having the largest representations.

2. Genetic diagnosis

SMA was diagnosed based on clinical symptoms and the results of genetic testing. Genetic testing was conducted in 95% (263/277) of the patients (type I, 99% [109/110]; type II, 97% [108/111]; type III, 95% [39/41]; type IV, 30% [3/10]; and SMARD1, 100% [1/1]). *SMN1* homozygous deletions were identified in 95% (250/263) of the genetically tested patients (type I, 94% [102/109]; type II, 98% [106/108]; type III, 97% [38/39]; and type IV, 0% [0/3]). Compound heterozygous variants in association with single copies of *SMN1* and single nucleotide variants were identified in 3% of type I cases. Point mutations were single nucleotide variants (c.188C>A,

Table 2. Genetic diagnosis.

type	performed	*SMN1* copy number		*SMN2* copy number			*NAIP* copy number	
	no. of cases (% of cases)	homozygous 0 copy	1 copy compound heterozygous	<2	3	4	0	>1
I (110)	109 (99%)	102	3*	51	7	0	40	33
II (111)	108 (97%)	106	0	1	38	1	9	73
III (41)	39 (95%)	38	0	1	11	11	0	10
IV (10)	3 (30%)	0	0	2	0	0	0	0
before the onset of symptoms (3)	3 (100%)	3	0	1	2	0	1	2
SAMRD1 (1)	1 (100%)	–	–	–	–	–	–	–
suspected (1)	0	–	–	–	–	–	–	–
total (277)	263 (95%)	250	0	55	58	12	50	118

c.188C>A (p.S63) and one copy; c.293G>A (p.C98Y) and one copy; c.826T>C (p.Y276H) and one copy.

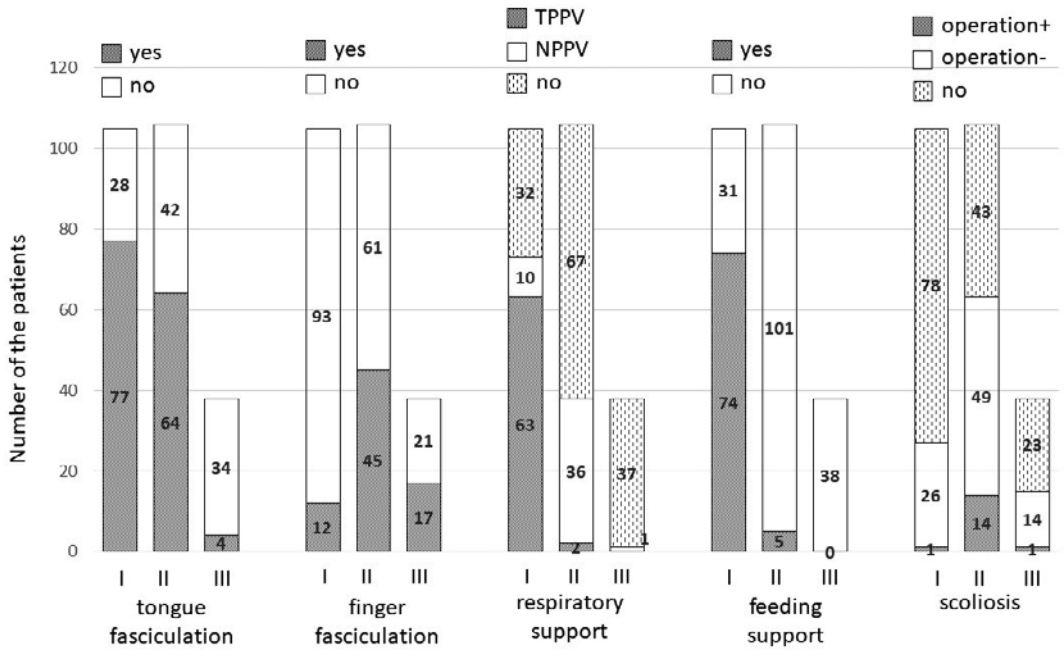


Figure 3. Clinical features of 5q spinal muscular atrophy.

c.293G＞A, and c.826T＞C; **Table 2**). Compound heterozygous variants (c.1537+1G＞A and C.1586G＞A) of *IGHMBP2* were identified in a SMARD1 patient.

3. Clinical features

Fourteen patients with type II and three patients with type III SMA had taken an intelligence test. The IQ of patients with types II and III SMA were 100.6 ± 20.8 and 118.3 ± 12.4 (mean ± SD), respectively (**Figure 2d**).

Tongue fasciculation was reported in 73% (77/105), 60% (64/106), and 11% (4/38) of patients with types I, II, and III SMA, respectively. Finger fasciculation was noted in 11% (12/105), 42% (45/106), and 45% (17/38) of patients with types I, II, and III SMA, respectively. Tracheotomy was performed in 60% (63/105) and 2% (2/106) of patients with types I and II SMA, respectively. Feeding support, nasogastric tube placement, and gastrostomy were performed in 70% (74/105) and 5% (5/106) of patients with types I and II SMA, respectively. Scoliosis was present in 26% (27/105), 59% (63/106), and 39% (15/38) of patients with types I, II, and III SMA, respectively. Surgery for scoliosis was performed in 4% (1/27), 22% (14/63), and 7% (1/15) of patients with types I, II, and III SMA with scoliosis, respectively (**Figure 3**, **Table S2**).

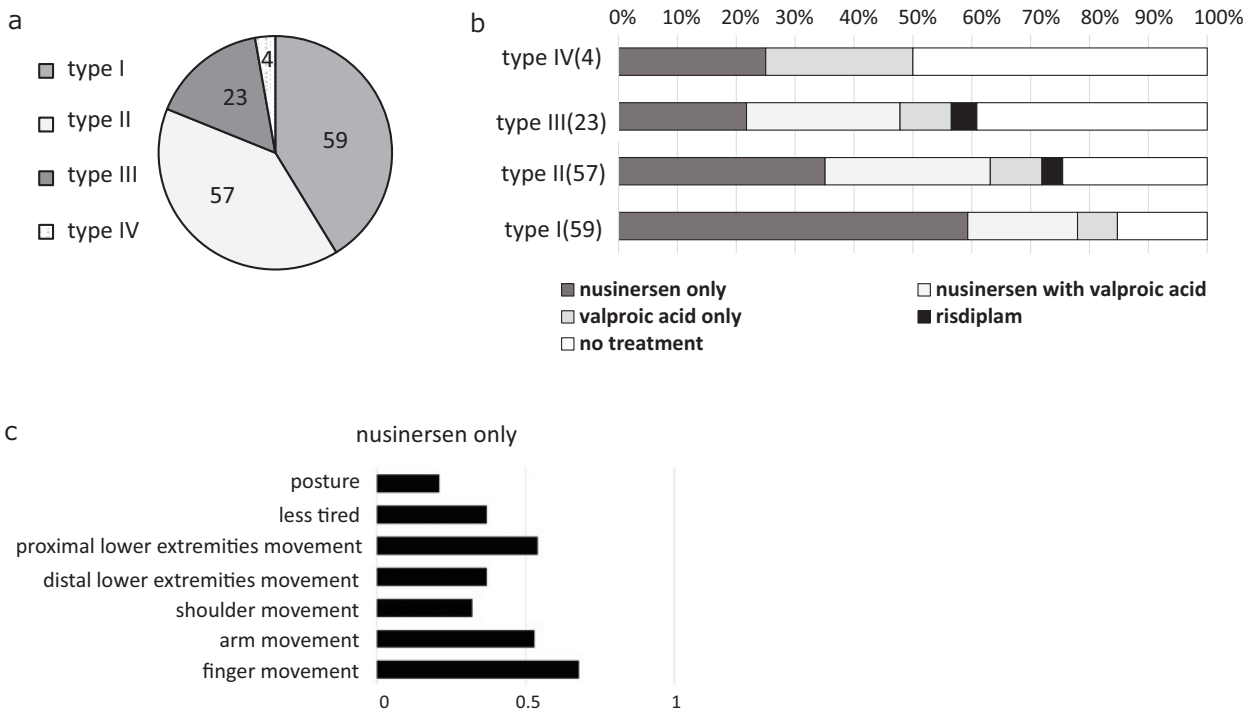


Figure 4. Questionnaire on therapeutic drugs.
a (upper left): Number of respondents by clinical type.
b (upper right): Presence, absence, and types of therapeutic drugs.
c (lower): Each effect of therapeutic drugs.

4. Questionnaire on therapeutic drugs

Of the 261 patients registered at the time of posting the questionnaires, 36 had unknown addresses; consequently, the questionnaires were sent to 225 patients, and 143 responses were obtained (type I, 59; type II, 57; type III, 23; and type IV, 4), representing a response rate of 64% (143/225; **Figure 4a**).

Of the patients who responded, 76% (109/143) were receiving treatment; 56% (61/109) were being administered nusinersen alone, 11% (12/109) valproic acid alone, 3% (3/109) risdiplam alone, and 30% (33/109) both nusinersen and valproic acid. By type, 85% (50/59), 75% (14/43), 61% (14/21), and 50% (2/4) of patients with types I, II, III, and IV SMA were following a treatment regimen (**Figure 4b**). More than half of the patients who received nusinersen alone or nusinersen + valproic acid (including those who reported using both valproic acid and nusinersen or had begun nusinersen after an interruption in valproic acid administration) reported improvements in finger, arm, and proximal lower extremity movements (**Figure 4c, S2**).

Discussion

1. Demographics

The data analyzed were obtained from the database of the registry of patients with SMA. The average age at registration in Cure SMA, one of the largest patient-reported SMA data repositories, was reportedly 7.0 months, 3.4 years, and 11.5 years for patients with types I, II, and III SMA, respectively. The average age at registration in our SMART consortium was higher than that in Cure SMA. This difference may be attributed to the year of starting registration (Cure SMA, 1996; SMART consortium, 2012).

2. Genetic diagnosis

The time from onset to genetic diagnosis was 0.3/0.3, 4.9/0.8, and 21/7.6 years (median/mean) for patients with type I, II, and III SMA, respectively. This showed that the less severe the clinical symptoms, the harder it was to make the diagnosis and the longer it took to be confirmed.[21] In particular, it has been shown that the diagno-

sis of type III SMA is often delayed, and the early diagnosis and treatment of patients with type III SMA is challenging.

Since *SMN1* and *SMN2* are homologous except for five bases, the identification of point mutations is difficult using the usual sequence identification methods alone. As a result, the number of reports of point mutations has been limited. We have reported a method to overcome this problem.[22] SMA with point mutations should be diagnosed without exception.[23,24]

3. Clinical symptoms

We previously reported the natural history of SMA using questionnaires sent to doctors[2]. By analyzing this registry, we confirmed our previously reported natural history of SMA. In particular, tongue fasciculation was common in patients with types I and II SMA, while finger fasciculation was common in patients with types II and III SMA. The site of fasciculation was thought to be the key to predicting the disease type. The proportions of patients with type I and II SMA requiring respiratory and feeding support were low compared to our previous report[2]. Probably after registration, many patients have gotten worsen and need feeding and respiratory support.

TREAT-NMD reported that the percentage of patients with type I SMA requiring invasive ventilation varied significantly between countries. For example, in some countries, reports suggest that no patients with SMA receive invasive ventilation, while in Italy, it is used in 13 out of 44 patients with type I SMA.[3] This variability might reflect differences in health care systems, availability of specialist care centers, physicians' personal preferences, or social and cultural considerations.[3] Since the SMART consortium aims to promote clinical trials, it is expected that patients enrolled in the consortium will be active in their treatment. On the other hand, patients who are reluctant to take treatment may not find a reason to enroll in the SMART consortium. When a tracheotomy becomes necessary due to respiratory muscle weakness, patients who are active in treatment are more likely to choose tracheotomy, while patients who are reluctant to undergo treatment are more likely to choose to live out their lives without tracheotomy.

In the same report,[3] 9% (439/5,068) of patients had feeding tubes (type I, 83% [366/439] and type II, 13% [57/439]). In SMART consortium, feeding tubes were inserted in 30% (79/262) of patients (type I, 70% [74/105] and type II, 5% [5/106]). Similar to invasive ventilation, there were variabilities in feeding support among countries (**Table 3**).

Scoliosis surgeries were performed in 9% (455/5,068) of patients (type I, 6% [27/455]; type II, 56% [254/455]; and type III, 38% [174/455]), as reported by TREAT-NMD. In SMART consortium, 6% [16/263] of patients underwent scoliosis surgery (type I, 1% [1/110]; type II, 13% [14/111]; and type III, 2% [1/41]). Scoliosis surgery was reported to be rare in patients with type I SMA, and most commonly utilized in patients with types II and III SMA. Similar results were found in SMART consortium. However, the proportion of patients who underwent surgery was low in all types.[3] Since SMART consortium lists the presence or absence of scoliosis surgery at the time of registration, we felt the information needed to be updated.

4. Questionnaire on therapeutic drugs

It is noteworthy that the proportion of patients receiving treatment is increasing. The proportion of patients undergoing treatment was 21% at the time of registration, but increased to 74% in June 2019. Many patients started treatment after registration. This is due to the remarkably rapid progress in developing treatments for SMA in recent years, with ongoing clinical trials and sustained marketing campaigns. In addition, progressive amelioration of the finger, arm, shoulder, and proximal lower extremity movements, as well as reduced fatigue, have been recognized by more than 30% of patients, confirming the efficacy of these treatments.

5. Registries

We started this registry at a time when SMA was untreatable with the intent to enroll patients in trials (**Figure 1**). Currently, therapeutic drugs are being developed, and patients are being registered by pharmaceutical companies (**Table S1**). However, it is difficult to share information among registries due to the need for the protection of personal information. In addition, each company only registers the information related to the medications that the pharmaceutical company is investigating and selling. Therefore, the information on the various

Table 3. Comparison with TREAT-NMD and Cure SMA.

	type	SMART consortium	TREAT-NMD*	Cure SMA**
total number		276	5,068	1,966 from total 6,583
average age at the time of registraion	I	3.3 y	N.D.	7 mo
	II	9.9 y	N.D.	3.4 y
	III	26.3 y	N.D.	11.5 y
average age at the time of diagnosis	I	6.2 mo	N.D.	5.2 mo
	II	70 mo	N.D.	22.1 mo
	III	289 mo	N.D.	97.8 mo
current age		0-1 y n=7 1-2 y n=8 2-5 y n=48 6-11 y n=94 12-19 y n=52 20-29 y n=24 30-39 y n=9 40-49 y n=8 50-59 y n=8 60-69 y n=4 70-y n=7	0-1 y n=284 1-2 y n=421 3-5 y n=424 6-9 y n=523 10-19 y n=654 20-29 y n=443 30-39 y n=400 40-49 y n=397 50-59 y n=167 60-69 y n=105 70-y n=32	N.D.
feeding tube	I	70%, n=74	n=439 (9%) type I n=366 type II n=57 type III n=18	N.D.
	II	5%, n=5		N.D.
respiratory support TPPV	I	60%, n=63	n=178 (4%) type I n=153 type II n=12 type III n=13	N.D.
	II	2%, n=2		N.D.
	III	n=0		N.D.
respiratory support NPPV	I	10%, n=10	n=437 (9%) type I n=250 type II n=127 type III n=60	N.D.
	II	34%, n=36		N.D.
	III	3%, n=1		N.D.
scoliosis surgery	I	1%, n=1	n=455 (9%) type I n=27 type II n=254 type III n=174	4%
	II	13%, n=14		91%
	III	3%, n=1		4%

* systemic review in August 2012.

** extending back from December 31, 2016 to January 1, 2010, the data of first contact to the Cure SMA.

treatments that have been administered to the patients throughout their lives is not available. Henceforth, a registry should be developed to provide a comprehensive view of all treatments that patients with SMA have taken in their lifetimes. SMART consortium aims to do this and will evolve to ensure that patients are registered and followed throughout their lives. Collaboration and information exchange between national registries, internationally integrated registries, and registries operated by pharmaceutical companies will be important, while paying utmost attention to the handling of personal information. For these reasons, in order to ensure the continuity of the registry and to enable the provision of optimal treatment to each individual, we are planning to join the Rare Disease Data Registry of Japan (RADDAR-J; https://www.raddarj.org/), which is an information integration platform that aggregates clinical information and information obtained from biological samples collected by the Japan Agency for Medical Development and the Intractable Disease Research Group of the Ministry of Health, Labour and Welfare.

Conclusion

The Japanese registry of patients with SMA is useful for elucidating the natural history of SMA and recruiting patients for clinical trials. It was also found that many patients are benefiting from the new treatments. SMART consortium is useful for understanding the natural history and current status of patients with SMA in Japan. As novel drugs are now being developed, SMART consortium has the potential to be a source of information on the clinical courses of patients throughout their lives, with both accuracy and continuity.

Data Statement: The data that support the findings of this study are available on reasonable request from the corresponding author, K.S. The data are not publicly

available in order to ensure the privacy of research participants.

Sources of Funding: This work was supported by Grants-in-Aid from the Research Committee of CNS Degenerative Diseases; Research on Policy Planning and Evaluation for Rare and Intractable Diseases; Health, Labour and Welfare Sciences Research Grants; and the Ministry of Health, Labour and Welfare of Japan. This research was supported by the Japan Agency for Medical Research and Development (grant number 21ek0109472h0002) and by the Japan Society for the Promotion of Science (KAKENHI grant number JP20K16610).

Conflicts of Interest: The authors declare that there are no conflicts of interest.

Author Contributions: All persons who meet authorship criteria are listed as authors, and all authors certify that they have participated sufficiently in the work to take public responsibility for the content, including participation in the concept, design, analysis, writing, and/or revision of the manuscript.

Acknowledgments: We thank to Ms. Akiko Ueda in charge of the administrative work of our registry.

Ethical Approval: 2556-R Institutional Review Board of Tokyo Women's Medical University (Shinjuku, Tokyo, Japan).

References

1. Pearn JH, Gardner-Medwin D, Wilson J. A clinical study of chronic childhood spinal muscular atrophy: a review of 141 cases. J Neurol Sci. 1978;38(1):23−37.
2. Kaneko K, Arakawa R, Urano M, et al. Relationships between long-term observations of motor milestones and genotype analysis results in childhood-onset Japanese spinal muscular atrophy patients. Brain Dev. 2017;39(9):763−73.
3. Bladen CL, Thompson R, Jackson JM, et al. Mapping the differences in care for 5,000 spinal muscular atrophy patients, a survey of 24 national registries in North America, Australasia and Europe. J Neurol. 2014;261(1):152−63.
4. Belter L, Cook SF, Crawford TO, et al. An overview of the Cure SMA membership database: Highlights of key demographic and clinical characteristics of SMA members. J Neuromuscul Dis. 2018;5(2):167−76.
5. Belter L, Cruz R, Jarecki J. Quality of life data for individuals affected by spinal muscular atrophy: a baseline dataset from the Cure SMA Community Update Survey. Orphanet J Rare Dis. 2020;15(1):217.
6. Jones CC, Cook SF, Jarecki J, et al. Spinal muscular atrophy (SMA) subtype concordance in siblings: findings from the cure SMA cohort. J Neuromuscul Dis. 2020;7(1):33−40.
7. Pechmann A, König K, Bernert G, et al. SMArtCARE-A platform to collect real-life outcome data of patients with spinal muscular atrophy. Orphanet J Rare Dis. 2019;14:1−6.
8. Mercuri E, Finkel R, Scoto M, et al. Development of an academic disease registry for spinal muscular atrophy. Neuromuscul Disord. 2019;29(10):794−9.
9. Finkel RS, Day JW, De Vivo DC, et al. RESTORE: A Prospective Multinational Registry of Patients with Genetically Confirmed Spinal Muscular Atrophy-Rationale and Study Design. J Neuromuscul Dis. 2020;7(2):145−52.
10. Waldrop MA, Kolb SJ. Current treatment options in neurology-SMA therapeutics. Curr Treat Options Neurol. 2019;21(6):25.
11. Elshafay A, Hieu TH, Doheim MF, et al. Efficacy and Safety of Valproic Acid for Spinal Muscular Atrophy: A Systematic Review and Meta-Analysis. CNS Drugs. 2019;33(3):239−50.
12. Mercuri E, Darras BT, Chiriboga CA, et al. Nusinersen versus Sham Control in Later-Onset Spinal Muscular Atrophy. N Engl J Med. 2018;378(7):625−35.
13. LoMauro A, Mastella C, Alberti K, et al. Effect of nusinersen on respiratory muscle function in different subtypes of type 1 spinal muscular atrophy. Am J Respir Crit Care Med. 2019;200(12):1547−50.
14. Finkel RS, Mercuri E, Darras BT, et al. Nusinersen versus sham control in infantile-onset spinal muscular atrophy. N Engl J Med. 2017;377(18):1723−32.
15. Mendell JR, Al-Zaidy S, Shell R, et al. Single-Dose Gene-Replacement Therapy for Spinal Muscular Atrophy. N Eng J Med. 2017;377(18):1713−22.
16. Day JW, Finkel RS, Chiriboga CA, et al. Onasemnogene abeparvovec gene therapy for symptomatic infantile-onset spinal muscular atrophy in patients with two copies of SMN2 (STR1VE): an open-label, single-arm, multicentre, phase 3 trial. Lancet Neurol. 2021;20(4):284−93.
17. Ratni H, Ebeling M, Baird J, et al. Discovery of Risdiplam, a Selective Survival of Motor Neuron-2 (SMN2) Gene Splicing Modifier for the Treatment of Spinal Muscular Atrophy (SMA). J Med Chem. 2018;61(15):6501−17.
18. Baranello G, Darras BT, Day JW, et al. Risdiplam in type 1 spinal muscular atrophy. N Engl J Med. 2021;384(10):915−23.
19. Munsat TL, Davies KE. International SMA consortium meeting. (26-28 June 1992, Bonn, Germany). Neuromuscul Disord. 1992;2(5-6):423−8.
20. Mercuri E, Finkel RS, Muntoni F, et al. Diagnosis and management of spinal muscular atrophy: Part 1: Recommendations for diagnosis, rehabilitation, orthopedic and nutritional care. Neuromuscul Disord. 2018;28(2):103−15.
21. Lin CW, Kalb SJ, Yeh WS. Delay in diagnosis of spinal muscular atrophy: a systematic literature review. Pediatr Neurol. 2015;53(4):293−300.
22. Kubo Y, Nishio H, Saito K. A new method for SMN1 and hybrid SMN gene analysis in spinal muscular atrophy using long-range PCR followed by sequencing. J Hum Genet. 2015;60(5):233−9.

23. Niba ETE, Nishio H, Wijaya YOS, et al. Clinical phenotypes of spinal muscular atrophy patients with hybrid *SMN* gene. Brain Dev. 2021;43(2):294−302.
24. Rochmah M Ar, Awano H, Awaya T, et al. Spinal muscular atrophy carriers with two *SMN1* copies. Brain Dev. 2017;39(10):851−60.