Chapter 11
Patient Registries for International Harmonized Clinical Development

En Kimura and Harumasa Nakamura

Abstract In this chapter, the role of patient registry and importance of the international harmonization to make a step toward progress in clinical development in orphan diseases are discussed. Remudy, Registry of Muscular Dystrophy, operated by the NCNP, National Center of Neurology and Psychiatry, Japan, runs two national registries for dystrophinopathy and GNE myopathy under the collaboration with the TREAT-NMD alliance. The aim of Remudy is to construct clinical research infrastructure and accelerate clinical development research for these rare diseases in Japan. We successfully disclose data sets for the feasibility studies in response to enquiries, send out appropriate information of clinical trials for the candidates to gear up for recruitment, as well as present the natural history and epidemiological data of the rare diseases with a new "registry-based" research style. Remudy provides a prototype of the clinical research infrastructure to overcome rare and incurable diseases.

Keywords Remudy • Patient registry • Rare disease • International harmonization • TREAT-NMD

11.1 Introduction

"Ichi-nichi mo hayaku" means "longing for the day" by Dr. Hisanobu Kaiya, administrative director of the Japanese Muscular Dystrophy Association, Corp., JMDA (http://www.jmda.or.jp), which is a slogan of the JMDA and also an official journal title of this 51-year-old patient's advocacy organization. To deliver curative treatment for patients and family of the rare, orphan, and incurable diseases is a wish of all concerned in this field. Based on the remarkable progress of basic research in molecular biology field, researchers have successfully clarified pathomechanism and achieved the "proof-of-concept" of treatment using animal models of the diseases. Following these successes, clinical applications of these results have been expected, related especially to molecular target strategies such as

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development of read-through agents [1] and exon-skipping therapies [2, 3] as curative treatments, which people really desire to be approved as the medication of the rare and incurable diseases, especially for Duchenne and Becker muscular dystrophies (DMD/BMD, dystrophinopathy). Actually, some clinical trials for new therapeutic strategies for dystrophinopathy are currently in operation or being planned. During the process, many challenges still exist in the planning and conducting of a clinical trial for rare diseases, in which dystrophinopathy is classified. The epidemiological data, the total number of patients, natural history, and clinical outcome measures are unclear or less well understood, although an adequate number of patients are needed to achieve significant results in clinical trials.

11.2 Rising of Global Tides of the Clinical Research Infrastructure Development with International Harmonization

To solve these problems, a patient registry is considered as an important infrastructure worldwide. In 2007, TREAT-NMD (*T*ranslational *R*esearch in *E*urope: *A*ssessment and *T*reatment of *N*euro*m*uscular *D*iseases), as a network of excellence for neuromuscular diseases, was established with the aim of "reshaping the research environment" in the neuromuscular field and to support translational research [4], by the original Sixth Framework Programme (FP6) grant from the European Union (EU) between 2007 and 2011. The National Institutes of Health (NIH) in the United States of America and the national institutes in Asian and Oceanian countries participated in TREAT-NMD. From 2012, it evolved into the international TREAT-NMD alliance with worldwide activity. TREAT-NMD developed a global database for DMD/BMD (dystrophinopathy) [5] and spinal muscular atrophy (SMA) patients [6] both in and out of Europe, to obtain epidemiological data, examine the total number of patients, determine the natural history of the disease, determine appropriate clinical outcome measures, collect adequate numbers of patients needed to achieve significant results in clinical trials, and inform patients of new drug development. This was achieved in part by the formation of a harmonized set of national DMD patient registries with a common data-sharing philosophy, comprising both new registries set up to follow the TREAT-NMD guidelines and existing national registries who agreed to follow them. Information collected follows a mandatory or highly encouraged set of questions agreed on by the TREAT-NMD global database oversight committee. As a result, information can be shared and compared between the different national registries, with the ultimate goal of all national registries eventually linking into a centralized global DMD registry. Actually, at the international level, the registries had been used for feasibility and recruitment in at least ten studies, following enquiries from researchers and industries.

As of 2014, in addition to DMD/BMD (dystrophinopathy) and SMA, the list of ten different disease patient registries was found on the TREAT-NMD website (http://www.treat-nmd.eu). Internationally, myotonic dystrophy (DM), congenital muscular dystrophies (CMD), congenital myasthenic syndrome (CMS), Charcot-Marie-Tooth disease (CMT), facioscapulohumeral muscular dystrophy (FSHD), hereditary inclusion body myopathy (GNE/HIBM), limb-girdle muscular dystrophy (LGMD) including fukutin-related protein (FKRP), myotubular and centronuclear myopathy (MTM/CNM), and dysferlinopathy are in operation.

11.3 Establishment and Operation of Japanese National Registry for Dystrophinopaty

In Japan, muscular dystrophy research groups have a history of close to 50 years, which were funded by the Nervous and Mental Disorders from the Ministry of Health, Labour, and Welfare (by March 2011) and are now by Intramural Research Grant for Neurological and Psychiatric Disorders of the National Center of Neurology and Psychiatry, Japan (NCNP, from April 2011), and achieved distinguished and world-leading researches in this field. To date, several Japanese dystrophinopathy databases have been developed; however, these have not been on a broad national scale. For instance, some were on a single-center basis, and others encompassed only a small local area or several hospital sites [7–9]. Some others were restricted to inpatients only [10]. Despite these early efforts, no national registry has been developed with the purpose of focusing on clinical trials.

In 2009, Dr. Mitsuru Kawai with his national research group and the NCNP developed a national registry of Japanese dystrophinopathy patients, Remudy (*Re*gistry of *Mu*scular *Dy*strophy) (http://www.remudy.jp/), in collaboration with the Japanese national muscular dystrophy research groups, 27 traditional muscular dystrophy wards, and hospitals belonging to the National Hospital Organization (NHO) and the NCNP, the Japanese Muscular Dystrophy Association, and finally the TREAT-NMD [11]. This project has been funded by the Nervous and Mental Disorders from the Ministry of Health, Labour, and Welfare (20B-12; between 2008 and 2011), and by Intramural Research Grant for Neurological and Psychiatric Disorders of the NCNP (23-4; 2011–2014, 26-7; 2014-) and supported by helpful cooperation with the JMDA. The development and management of the registry is led by the principal investigator of the Japanese muscular dystrophy research group. Steering committee members include scientists, clinicians, and representatives of patient organizations. The registry office was set up in the NCNP. The purpose of this registry was to effectively recruit eligible patients to new clinical trials and provide timely information to patients about upcoming trials. The data included clinical and molecular genetic information as well as all items required for the TREAT-NMD global patient registry. Registry data also provides more detailed

knowledge about the natural history and epidemiology of the disease, as well as information about clinical care.

The database includes dystrophinopathy patients whose genetic status was confirmed by genetic analysis throughout Japan. As the cost of sequencing analysis of the DMD gene is not covered by the public health insurance in Japan, for patients who intend to register but are not genetically confirmed by the multiplex ligation-dependent probe amplification (MLPA) for *dystrophin* gene, Remudy provides free service of sequencing analysis of the *dystrophin* gene. Information about the registry was provided to interested individuals, who could easily access to the "case report form" and the "informed consent form" in the Remudy website or at the registry office. Provision of all data by patients is voluntary and is not 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 they may be removed from the registry immediately on request. It was stated that refusal to participate would not affect the subsequent medical care of the patient. The National Center of Neurology and Psychiatry Ethics Committee approved this registration system. Data obtained via the registry form included clinical symptoms, results of biochemistry, muscle biopsy, other laboratory analysis, and description of the genetic mutation. Epidemiological information provided includes walking capability, cardiac and respiratory functions, serum creatine kinase, history of scoliosis surgery, and steroid therapy status. All items were confirmed by their attending physicians and, finally, by molecular and clinical curators in Remudy (three active molecular and clinical curators each). Information was annually updated by registrant's self-report with their physician's confirmation following reminder from registration office. To decide whether a patient was classified as DMD or BMD, first, the attending physician made a diagnosis whether a patient was DMD or BMD by the clinical and molecular information. Then, our clinical and genetic curators double-checked their classification by reviewing clinical information and also data from pathological (including dystrophin immunohistchemical staining, if applicable) and genetic analysis.

As of May 2014, 1,293 patients were registered in the Remudy dystrophinopathy registry from all over Japan (Figs. 11.1 and 11.2). To analyze the data from July 2009 to May 2014, information of 1,173 patients were confirmed by the curators. Data from 1,171 patients, who agreed to participate in this study, were analyzed. It comprises of 940 DMD, 201 BMD, and 30 IMD patients, respectively (Fig. 11.3). All the registrants in Remudy database got genetic diagnosis as dystrophinopathy by MLPA for *dystrophin* gene and/or direct sequencing analysis of the *dystrophin* gene which was provided by Remudy. At the end of December 2013, we have well analyzed the *dystrophin* gene in 340 out of 342 cases. In case of single exon deletion/duplication reported by the MLPA methods, the corresponding exon and the neighbor exons were sequenced (41 %). In case of no deletion/duplication reported by the MLPA methods, whole 79 exons were sequenced (59 %). Based on the precise curation system, distribution of mutation in the registrants with dystrophinopathy was shown in Table 11.1. Most frequent mutation was deletion (60.6 % of DMD, 76.9 % of BMD, and 47.1 % of IMD). Second frequent was other

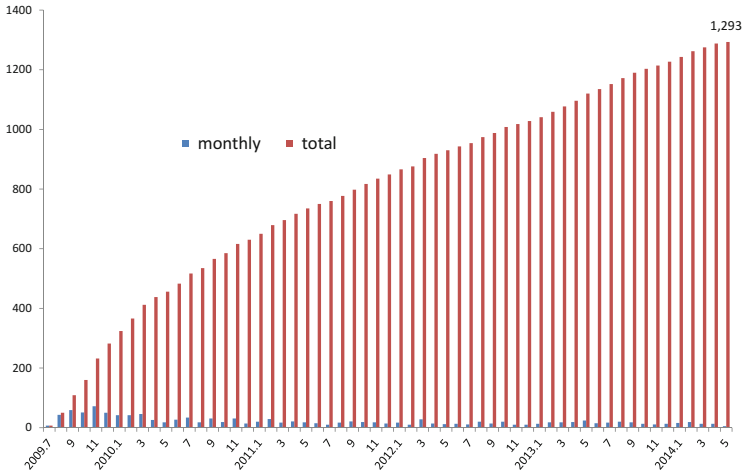

Fig. 11.1 Number of registrants in Remudy national dystrophinopathy registry. As of May 2014, 1,293 patients were registered in this national registry from all over Japan. *Blue bars* show monthly registered number; *red bars* show total number accumulated since the start of the registry. Total number of registrants is still increasing

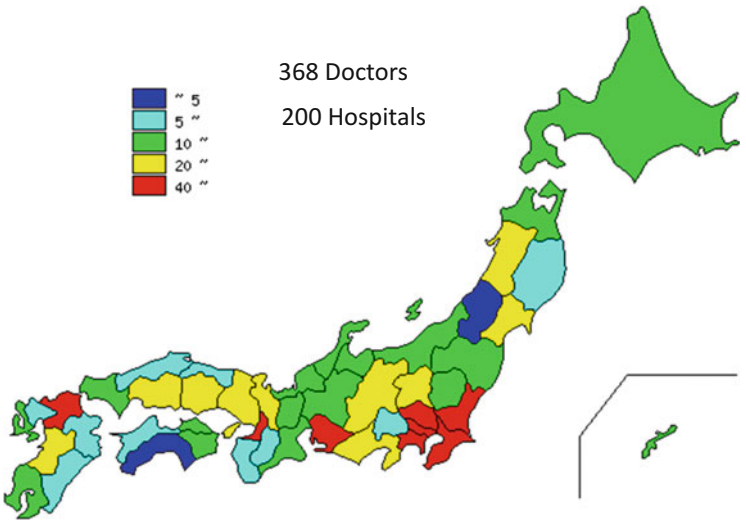

Fig. 11.2 Prefectural distribution of registrants in Remudy national dystrophinopathy registry. Dystrophinopathy patients from every prefecture in Japan are registered in this registry by cooperation of 368 doctors in 200 hospitals. Most registrants were concentrated in populated area: Fukuoka, Osaka, Aichi, and Kanto region

mutations (24.3 % of DMD, 16.2 % of BMD, and 23.5 % of IMD) which included nonsense mutations, small insertion/deletion mutations, deep intronic mutations, and splice site mutations. Then third frequent was duplication (13.6 % of DMD,

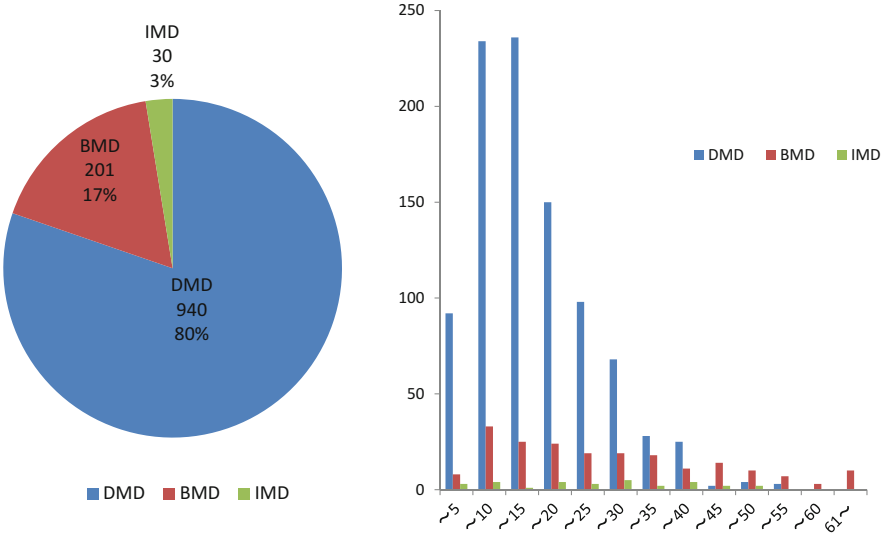

Fig. 11.3 Diagnosis and age distribution of registered individuals. Data from 1,171 patients who have agreed to participate in this study and confirmed by molecular and clinical curators were analyzed. It comprises of 940 (80 %) DMD, 201 (17 %) BMD, and 30 (3 %) IMD patients, respectively. Most registrants are under 20 years of age, but those over 35 years with DMD are also registered

Table 11.1 Distribution of mutation in the registrants with DMD and BMD

	DMD		BMD		IMD	
	Number	%	Number	%	Number	%
Distribution of mutation						
Deletion	388	60.6	90	76.9	8	47.1
Duplication	87	13.6	6	5.1	5	29.4
Others[a]	163	24.3	19	16.2	4	23.5
Deletion and duplication	1	0.2	0	0.0	0	0.0
No mutation found[b]	1	0.2	2	1.7	0	0.0
	640	100	117	100	17	100

[a]Others include nonsense mutations, small insertion/deletion mutations, deep intronic mutations, and splice site mutations
[b]The diagnosis was confirmed based on their pathological findings in muscle biopsy including a negative immunohistochemical staining against dystrophin

5.1 % of BMD, and 29.4 % of IMD, Fig. 11.3). Clinical features of Japanese dystrophinopathy patients are shown in Table 11.2, which are available on the Remudy website to all concerned, including patients, family, and doctors who care for the dystrophinopathy patients, for download. Frequency of individual exon deletions was shown in Fig. 11.4.

Remudy already supplied the epidemiological data for 11 feasibility studies, and provided timely information about two independent clinical trials to registrants who

Table 11.2 Clinical manifestations of Japanese dystrophinopathy patients in Remudy database

	DMD		BMD		IMD	
	Number	%	Number	%	Number	%
Walking capacity						
Normal walking	328	40.2	125	74.4	7	26.9
Not able to walk and sit without support	252	30.9	38	22.6	10	38.5
Not able to sit without support	229	28.1	5	3.0	9	34.6
Before development	6	0.7	0	0.0	0	0.0
Cardiac function						
Normal	516	63.3	120	71.4	13	50.0
Dysfunction	277	34.0	47	28.0	13	50.0
Not performed	22	2.7	1	0.6	0	0.0
Respiratory function						
Normal	619	76.0	163	97.0	17	65.0
Dysfunction	162	20.0	3	2.0	6	23.0
Not performed	34	4.0	2	1.0	3	11.0
Steroid use						
Current	264	32.4	8	4.8	6	23.1
Used to	103	12.6	6	3.6	3	11.5
Never	447	54.8	154	91.7	17	65.4
Total	815	100	168	100	26	100

Detailed information is available on the Remudy website (http://www.remudy.jp)

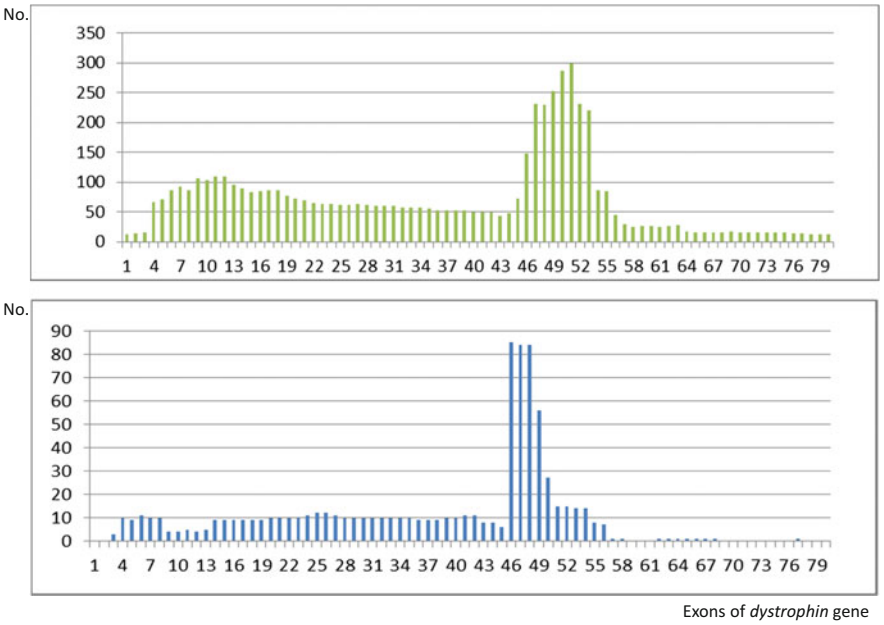

Fig. 11.4 Frequency of individual exon deletions. The distribution of exon deletion shows common hot spot regions in exon 45–54 in DMD and BMD

might be eligible for upcoming clinical trials, and accelerated the effective recruitment of eligible patients as expected. To inform the public of the activity of Remudy, we sent a paper version of "Remudy news," "Remudy news letter" by e-mail, and frequently renewed news page on Remudy website. Remudy news volume 11 was published with 1,781 copies in June 2014, Remudy news letter volume 50 was sent out to 648 subscribers, and the Remudy website traffic count was 1,845 during June 2014. We also hosted local lecture meetings for medical experts and patients all over Japan. In 2013, we sent out the questionnaires for medical providers throughout Japan in 2013 to clarify how Remudy was well known. We found nearly 75 % of medical providers knew about the Remudy activity.

11.4 Importance of Clinical Research Arisen from Registry Data Analysis

This registry data also provides more detailed knowledge about natural history, epidemiology, and clinical care. Especially, a natural history data regarding ambulation of DMD patients in 2013 was reported to solve a research question which arose from the Japanese DMD guideline committee [12]. In this study, we evaluated

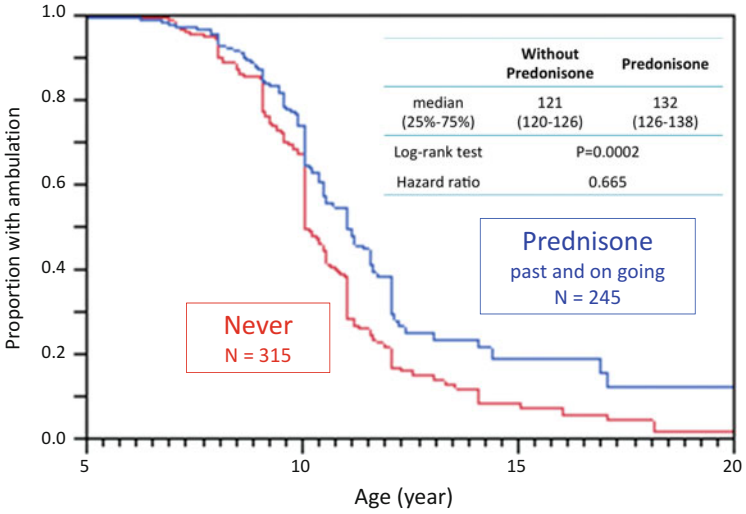

Fig. 11.5 Long-term efficacy of prednisolone (PSL) for prolonging ambulation among genetically confirmed DMD patients in Japanese dystrophinopathy national registry (Remudy). Of the 560 patients included, 245 (43.8 %) were in PSL treatment group, and 315 (56.2 %) were without PSL treatment. Both groups consist of ambulant patients aged 5, 10, and 15 years, and the number breakdown by age was 242, 136, and 8 for the PSL treatment group and 311, 145, and 10 for without-PSL group, respectively. The median age at loss of ambulation was 10.1 years for the patients in without-PSL treatments group and 11.0 years in the PSL treatment group. Patients treated with PSL were able to ambulate significantly 11 months longer than those without PSL

the long-term efficacy of prednisolone (PSL) for prolonging ambulation among 560 Japanese DMD patients who were genetically confirmed. The time of loss of ambulation in patients with prednisolone (PSL) treatment (n = 245) was 11 months longer than that of those without PSL treatment (n = 315) (Fig. 11.5). This is the largest cross-sectional objective study in the world. This research spun off into another survey research to ask the effective resume of steroid treatment for DMD, such as dosage, intervals, starting age, and adverse side effect if any, since there was no registry item regarding these.

In our research group, Dr. Kawai estimated the number of DMD patients in Japan would be about 3,500 at the end of March 2013, according to the annual numbers of boy's birth data in Japan and the life chart data of DMD from the NHO hospital database, which closed to the number expected from Akita prefecture's data on Remudy. This information is frequently asked and needed by pharmaceutical companies when considering new products for DMD and also demanded by persons in charge of neuromuscular field in the regulatory agency, Pharmaceuticals and Medical Devices Agency, Japan.

11.5 Applications of the Registry for Other Hereditary Neuromuscular Disorders and Establishment of Gene Analysis System for Them in Japan

GNE myopathy (distal myopathy with rimmed vacuoles, DMRV): GNE myopathy is one of the ultra-rare diseases. In more than 300 GNE myopathy cases, we have analyzed the GNE gene (63 cases between January and December of 2013) and have found 41 % of confirmed homozygote or compound heterozygote, 3 % of single mutation on single allele, and 51 % of no mutation [13]. Some frequent mutations in GNE gene were found. The national registry for GNE myopathy in Japan was launched in June 2012 (http://www.remudy.jp/dmrv/index.html). As of June 2014, 155 GNE myopathy candidate registrants were accepted. More detailed information of this registry was described in Chap. 10.

Fukuyama congenital muscular dystrophy (FCMD): FCMD is the second most prevalent form of muscular dystrophy in Japan. The FCMD registry was established by the JMDA on October 2011 (http://www.jmda.or.jp/kiko/). By January 23, 2014, 165 candidate registrants were accepted. Every year, the questionnaires for registrants were sent out, and those results were reported at the research group meeting and JMDA website and then were reflected to the activity of the branch meeting for FCMD patients in the JMDA.

Myotonic dystrophy and other myotonia syndromes: The arrangement meeting for the myotonic dystrophy registry started at February 2012. We have planned the curators training, set up the registry items, and collected and regulated experts' opinions. We prepared the DM registry office at the Department of Neurology, Osaka University. The application of DM registry has been reviewed by the ethical committee in Osaka University and is currently under review at the NCNP. DM registry will be launched in October 1, 2014. This DM registry may cover other myotonia syndromes. The advanced gene analysis methods for Myotonic dystrophy type 1 and 2 were also examined in the NCNP.

Spinal muscular atrophy (SMA): SMA registry was launched in August 2012 and run by the Institute of Medical Genetics, Tokyo Women's Medical University (Prof. Kayoko Saito, http://www.sma-rt.org). As of July 2013, more than 100 candidate registrants were accepted.

Oculopharyngeal muscular dystrophy (OPMD): The *PABPN1* gene mutations were detected in 99 patients (84 families), according to Dr. Narihiro Minami in the NCNP [14]. The opposite correlation was found between GCN repeat numbers and the age of onset. Japanese OPMD national registry is now in preparation with nationwide collaboration.

Dysferlinopathy (Miyoshi myopathy, limb-girdle muscular dystrophy type 2B, LGMD2B, anterior tibial myopathy): Dr. Toshiaki Takahashi in the NHO Sendai Nishitaga National Hospital reported that 42 independent mutations among affected 91 families were determined by PCR-SSCP method and then 31 independent mutations among affected 45 families by whole 55 exon sequencing method [15]. Also, the next-generation sequencing for dysferlinopathy, considered as a

useful tool as well as for other LGMD, will be ready to use in several institutes in Japan. Dysferlinopathy national registry is also planned with Remudy research group.

In addition, registries for congenital muscular dystrophies (CMD) [16], congenital myasthenic syndrome (CMS) [17], facioscapulohumeral muscular dystrophy (FSHD) [18], and limb-girdle muscular dystrophy (LGMD) have been planned as well.

Preparation of the new advanced web registration system: We studied safe and efficient way of patient self-registry and developed a new web-based registration system under collaborations with Hitachi Solutions, Ltd. Because of high-standard security within ethical guidelines, in addition, stability, and applicability, this excellent system will be useful for other rare diseases as well as many common disorders.

11.6 International and Nationwide Research Harmonization for Rare Diseases

From 1999, the Cooperative International Neuromuscular Research Group (CINRG) was developed as a consortium of medical and scientific investigators from over 20 international academic and research centers. The CINRG coordinating center is located in the Children's Research Institute of Children's National Medical Center in Washington, DC, USA. The goal of CINRG is to contribute to the research and the treatment of neuromuscular diseases by studying the causes, pathogenesis, and clinical outcomes of the diseases and also by conducting well-controlled clinical studies that examine promising therapeutic interventions that may improve or extend quality of life for patients. To date, CINRG has completed six [19, 20] and is currently running four clinical studies. Both in and out of Europe, TREAT-NMD alliance has developed a global database for dystrophinopathy patients to promote clinical trials for new therapeutic strategies, as tools to study the epidemiology [5], burden of the DMD [21], as well as other neuromuscular disorders, as described above. CARE-NMD (http://en.care-nmd.eu), a European project improving care for DMD, led by Dr. Janbernd Kirschner, Freiburg University, part-funded by the EU between May 2010 and April 2013, brought together leading care centers to disseminate information about best-practice DMD care and to implement international consensus care standards. The CARE-NMD patient survey of care and quality of life to the national dystrophinopathy registries across seven partner countries in EU, already collecting almost 1,100 responses, expanded to other national registries belongs to TREAT-NMD, internationally. In 2013, the CARE-NMD family survey in Japan was carried out under collaboration with CARE-NMD project and the Muscular Disease Center at the NCNP directed by Dr. Hirofumi Komaki. This survey presented the current conditions and problems of DMD patients and families, clarified some similarities and differences among the

countries including western and eastern European countries and Japan, and was also useful for providing the patients information about the care and cure for DMD.

We have also discussed the role of the Remudy as a prototype among the rare disease infrastructure for the clinical research. We participated in every related meetings, such as the meeting for rare and intractable diseases held every other month with the concerned persons in some pharmaceutical companies and the preparation meetings for patient registries in January and February 2013, led by Dr. Tomonori Tateishi (former NCNP, present PMDA). In the first international workshop in Japan for rare disease registries in July 2013, the international key speakers from Europe, the United States, and China were invited, and domestic speakers working for each patient registry discussed the collaboration among the rare disease registries, followed by a second domestic workshop for rare disease registries in July 2014, both managed by Dr. Hiroshi Mizushima and our group (http://www.remudy.jp). At the symposium in the 34th Annual Meeting of The Japanese Society of Clinical Pharmacology and Therapeutics, we discussed the roles and the recent status of patient registries in clinical research in Japan. Among these activities, we confirmed importance of the harmonization of patients and families, medical providers, and other stakeholders, such as pharmaceutical industries, researchers, patient advocacies, and the regulatory agency.

11.7 Discussion and Plan for Next Step

Today in the drug development field, operation of international clinical trials have been discussed across the world. In Japan, various international trials have already been done or are in operation. Information regarding adequate dosage, administration, efficacy, and safety of the candidate agents in Japanese people are important for review and approval in Japan, even though clinical trials do not have to be done as international trials. It was impossible to recruit participants who met inclusion criteria of each study in a single country. For example, 174 nonsense mutation DMD patients participated in an international late phase II trial for ataluren (PTC124, Translarna™), and more than 300 DMD patients who had particular mutation altered by exon 51 skipping therapy from 25 countries participated in 5 clinical trials to develop drisapersen. Now, it is an important strategy to plan and operate international harmonization at the early phase of development and to investigate racial variation of drug efficacy and safety concurrently in many hereditary neuromuscular diseases, which are classified into rare diseases. At the present day, some other international clinical trials for DMD patients are running, such as phase II/III study of coenzyme Q10 and lisinopril and phase III study of tadalafil. Domestic clinical trials for unique drug development in Japan are also running such as phase II study of arbekacin sulfate (NPC-14) as a read-through agent and exploratory study of NS-065/NCNP-01 as an exon 53 skip agent. In addition, clinical development of medical devices draws an awful lot of attention at

the moment. One major example is the currently ongoing multicenter clinical trial of a robot suit HAL being designed as a tool for neuromuscular rehabilitation.

Recently, in June 2014, Prosensa, a leading company developing exon-skipping agents for DMD, announced regulatory path forward for drisapersen as a potential treatment for DMD, with a plan to submit a new drug application to the FDA in 2014. Dialogue with EMA continues with the intent to seek approval. In August 2014, PTC Therapeutics received conditional approval in the EU for Translarna™ (ataluren) for the treatment of nonsense mutation DMD.

To conclude, Remudy, the patient registry for the neuromuscular disorders, is the first national registry for rare diseases including both clinical and molecular information in Japan to lead to the clinical developmental studies and to enable revealing nationwide epidemiological data. We run the Remudy successfully so far, because of the accurate gene analysis system, cooperation of patients, families, advocacy groups, medical providers, and carefully planned operation system including the steering committee as well as international collaboration. We continue to run this system, to expand the target diseases, and to step forward to develop a new system covering the whole rare and intractable diseases with other research groups. The patient registries are now recognized as a useful tool to accelerate clinical research of various rare diseases. Further, we will promote this infrastructure for clinical research to complement the pitfall of the national intractable disease registries now being planned as one of the effective measures to overcome the diseases by the Ministry of Health, Labour, and Welfare, Japan, especially prepared for deduction of patient's medical expenses. Our proposed new registry system will make the healthcare administration of the government more satisfactory.

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