Brain & Development 42 (2020) 277–288

BRAIN & DEVELOPMENT
Official Journal of the Japanese Society of Child Neurology

www.elsevier.com/locate/braindev

Original article

Clinical practice with steroid therapy for Duchenne muscular dystrophy: An expert survey in Asia and Oceania

Fumi Takeuchi [a], Harumasa Nakamura [a,*], Naohiro Yonemoto [b], Hirofumi Komaki [a,c], Raymond L. Rosales [d], Andrew J. Kornberg [e], Allan H. Bretag [f], Charungthai Dejthevaporn [g], Khean Jin Goh [h], Yuh-Jyh Jong [i,j], Dae-Seong Kim [k], Satish V. Khadilkar [l], Dingguo Shen [m], Kum Thong Wong [n], Josiah Chai [o], Sophelia Hoi-Shan Chan [p], Sara Khan [q], Ohnmar Ohnmar [r], Ichizo Nishino [s], Shin'ichi Takeda [t], Ikuya Nonaka [c,s]

[a] *Department of Clinical Research Support, Translational Medical Center, National Center of Neurology and Psychiatry, 4-1-1 Ogawa-higashi, Kodaira, Tokyo 187-8551, Japan*
[b] *Department of Biostatistics, Kyoto University School of Public Health, Yoshidakonoe, Sakyo, Kyoto, Kyoto 606-8501, Japan*
[c] *Department of Child Neurology, National Center Hospital, National Center of Neurology and Psychiatry, 4-1-1 Ogawa-higashi, Kodaira, Tokyo 187-8551, Japan*
[d] *The Department of Neurology & Psychiatry and The NeuroScience Institute, University of Santo Tomas Hospital, España Blvd, Sampaloc, Manila, 1008 Metro Manila, Philippines*
[e] *Children's Neuroscience Centre, The Royal Children's Hospital Melbourne, 50 Flemington Road, Parkville, Victoria 3052, Melbourne, Australia*
[f] *School of Pharmacy and Medical Sciences, University of South Australia, Adelaide, SA 5001, Australia*
[g] *Department of Medicine, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok 10400, Thailand*
[h] *Division of Neurology, Department of Medicine, Faculty of Medicine, University of Malaya, 50603 Kuala Lumpur, Malaysia*
[i] *Departments of Pediatrics and Laboratory Medicine, Kaohsiung Medical University Hospital/Graduate Institute of Clinical Medicine, College of Medicine, Kaohsiung Medical University, Taiwan 100, Shih-Chuan 1st Rd, Kaohsiung 80708, Taiwan*
[j] *College of Biological Science and Technology, National Chiao Tung University, 75 Po-Ai St, Hsinchu 30068, Taiwan*
[k] *Department of Neurology, Pusan National University Yangsan Hospital, 20 Kumo-ro, Yangsan, Gyeongnam, Republic of Korea*
[l] *Department of Neurology, Bombay Hospital Institute of Medical Sciences, 12, Marine Lines, Mumbai, Maharashtra 40020, India*
[m] *Fudan University, 220 Handan Rd, WuJiaoChang, Yangpu District, Shanghai 200433, China*
[n] *Department of Pathology, Faculty of Medicine, University of Malaya, 50603 Kuala Lumpur, Malaysia*
[o] *Department of Neurology, National Neuroscience Institute, 11 Jalan Tan Tock Seng, Singapore 308433, Singapore*
[p] *Division of Paediatric Neurology, Department of Paediatrics and Adolescent Medicine, Queen Mary Hospital, The University of Hong Kong, Hong Kong Special Administrative Region*
[q] *Department of Neurology, Aga Khan University Hospital, Stadium Rd, Karachi, Karachi City, Sindh 74800, Pakistan*
[r] *Department of Medical Neurology, University of Medicine 1, No. 245, Myoma Kyaung Street, Lanmadaw Township, Yangon, Myanmar*
[s] *Department of Neuromuscular Research, National Institute of Neurosciences, National Center of Neurology and Psychiatry, 4-1-1 Ogawa-higashi, Kodaira, Tokyo 187-8551, Japan*
[t] *Department of Molecular Therapy, National Institute of Neuroscience, National Center of Neurology and Psychiatry, 4-1-1 Ogawa-higashi, Kodaira, Tokyo 187-8551, Japan*

Received 7 July 2019; received in revised form 4 December 2019; accepted 6 December 2019

Abbreviations: AOMC, Asian and Oceanian Myology Centre; BMD, Becker muscular dystrophy; DFZ, Deflazacort; DMD, Duchenne muscular dystrophy; DXA, Dual-energy X-ray absorptiometry; PSL, Prednisolone/prednisone; SAR, Strategic Administrative Region; TREAT-NMD, Translational Research in Europe – Assessment & Treatment of Neuromuscular Diseases

* Corresponding author.
E-mail address: hnakamura@ncnp.go.jp (H. Nakamura).

https://doi.org/10.1016/j.braindev.2019.12.005

Abstract

Background: Several studies on clinical practice for Duchenne muscular dystrophy (DMD) have been conducted in Western countries. However, there have been only a few similar studies in Asia and Oceania. Here, we investigate the steroid therapy-related clinical practice for DMD among the local experts. In 2015, we conducted a DMD expert survey in Asia and Oceania to acquire information regarding patients with DMD and to assess current clinical practice with the cooperation of Asian and Oceanian Myology Centre, a neuromuscular disease research network.

Results: We obtained survey responses from 87 out of 148 clinicians (62%) from 13 countries and regions. In China, 1385 DMD patients were followed-up by 5 respondent neurologists, and 84% were between 0 and 9 years of age (15% were 10–19 years, 1% > 19 years). While in Japan, 1032 patients were followed-up by 20 clinicians, and the age distribution was similar between the 3 groups (27% were 0–9 years, 35% were 10–19 years, 38% were >19 years). Most respondent clinicians (91%) were aware of DMD standard of care recommendations. Daily prednisolone/prednisone administration was used most frequently at initiation (N = 45, 64%). Inconsistent opinion on steroid therapy after loss of ambulation and medication for bone protection was observed.

Conclusions: Rare disease research infrastructures have been underdeveloped in many of Asian and Oceanian countries. In this situation, our results show the snapshots of current medical situation and clinical practice in DMD. For further epidemiological studies, expansion of DMD registries is necessary.

Keywords: Duchenne muscular dystrophy; Steroid therapy; Clinical practice; Epidemiology; Care recommendation; Asian and Oceanian Myology Center

1. Introduction

Duchenne muscular dystrophy (DMD) is a rare chromosome X-linked disease that affects 1 in 5000–6000 newborn boys [1]. The disease follows a progressive course of muscle weakness, including the respiratory and cardiac muscles. Affected boys lose the ability to ambulate independently by the age of 12 years [2]. Although multiple treatment strategies are under investigation and have shown promise for DMD [3,4], corticosteroids remain the only drugs with objective confirmed effects on muscle weakness [5].

Steroid therapy can alter the course of DMD, improve muscle function, and prolong walking ability for 2–5 years [6]. Beneficial effects of steroids are also observed after loss of ambulation, in terms of a reduced incidence of scoliosis and a slower decline in upper extremity and cardiorespiratory functions [6]. Indeed, international guidelines for DMD treatment recommend prednisolone and/or prednisone (PSL) (0.75 mg/kg/day) and deflazacort (DFZ) (0.9 mg/kg/day), which are recognized to be most effective in the short term [7].

However, long-term daily steroid regimens are associated with various side effects, such as obesity, behavioural changes, low stature, and bone fractures [8]; several investigations into the optimal timing, dose, and regimen of steroid therapy are ongoing. Alternative dosing regimens, such as weekend dosing (10 mg/kg/week divided over 2 weekend days) [9], lower doses [10], and alternate-day doses [11–13], have been reported, but there is currently no consensus on which method offers the most effective treatment with the fewest side effects [14]. It has been reported that the regimens used in practice still vary in Japan, as well as in Western countries [15–19], all of which might have been recommended by experts in the past.

Several studies on the current clinical practice for DMD, using registries of the patients, have been reported from Western countries [16,20,21]. However, there have been only a few of such studies from Asian and Oceanian countries [19,22–25]. We conducted an international survey of clinicians in collaboration with the Asian Oceanian Myology Center (AOMC) to elucidate the epidemiology and clinical practice in these countries.

2. Methods

2.1. Study population and recruitment

The AOMC was established in 2001 to facilitate scientific communication and collaboration in the neuromuscular disease field in Asian and Oceanian countries. As of 2016, the AOMC executive board consisted of 37 experts from 15 countries and regions in Asia and Oceania (Australia, China, China Hong Kong Special Administrative Region [SAR], India, Iran, Japan, Malaysia, Myanmar, New Zealand, Pakistan, Philippines, Singapore, South Korea, Taiwan and Thailand). The AOMC membership became the target clinician survey population as they are the known experts/referral centre heads in the field and are likely to have

the largest clientele to capture DMD cases in their locale.

We enrolled local experts and/or clinicians who manage patients with DMD from these regions, by requesting that the AOMC executive board members nominate potential participants who may meet our inclusion criteria. We included clinicians who: 1) had experience in treating patients with DMD, and 2) were able to reply to the questionnaire in English. In Japan, we enrolled study participants via the Muscular Dystrophy Clinical Trial Network [26].

Responses were collected electronically using SurveyMonkey or by email or postal mail between December 2015 and June 2016. Responses by mail were entered into SurveyMonkey upon receipt. Data analysis was conducted in Microsoft (Redmond, WA, USA) Excel 2016.

2.2. Questionnaire

The survey consisted of 3 questions of respondent's background, 15 questions of clinical practice on DMD and 2 questions of others. Questions regarding a respondent clinician's clinical practice for DMD probed: 1) the number of patients with DMD grouped by age (0–9, 10–19, >19 years), 2) awareness of DMD care recommendations published in 2010 [27,28], 3) steroid therapy experience, 4) timing of steroid therapy initiation, 5) steroid therapy usage after the patient's loss of ambulation, 6) experience of side effects leading to withdrawal of steroid therapy, 7) assessment of and medication for bone health with steroids, and 8) the steroid regimen used at initiation and for maintenance.

We extracted responses from the clinicians who had steroid therapy experience, and analysed their habits and practices regarding steroid usage (steroid therapy for patients with loss of ambulation, bone assessment, medication for bone protection, and steroid regimen) by country. Among the question items above, item 8 (steroid regimen used at initiation and for maintenance) alone was analysed only for physicians currently prescribing steroids whereas responses to all other questions were compared among all physicians with any history of prescribing steroids.

3. Results

3.1. Demographics

Fig. 1 shows the study flow chart. In July 2015, we contacted the AOMC executive board members of 15 countries and regions to acquire their agreement to the study and to obtain their cooperation in nominating eligible clinicians in their country. The executive board members of 13 countries and regions agreed with the study and nominated 148 clinicians. (The other 2 countries and regions did not respond to our inquiry.) Surveys were sent to all 148 clinicians with a response rate of 62% (87 clinicians). Respondent characteristics are summarized in Table 1.

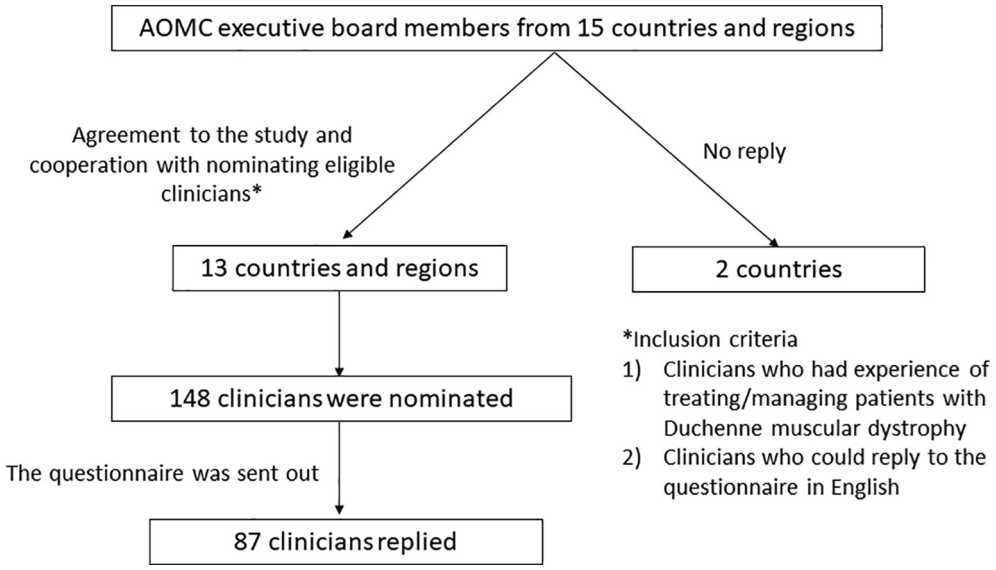

Fig. 1. Study flow chart. We contacted Asian Oceanian Myology Center (AOMC) Executive Board Members in 14 Asian and Oceanian countries to ask for their agreement of this study and their cooperation of nominating potential participants who might meet our inclusion criteria. Inclusion criteria were: 1) those who have experience seeing Duchenne muscular dystrophy (DMD) patients, and 2) those who could reply to the questionnaire in English. The members in 13 countries agreed, nominated 148 clinicians, and provided their personal information (name, affiliation and email-address). Then, we sent out our questionnaire to the 148 clinicians and 87 clinicians replied.

Table 1
Demographics of the study participants.

Country	Sent out (*N*)	Valid reply (*N*, [%])	Specialty				Affiliation			
			Pediatrics/child neurology	Neurology	Genetics	Other	University Hospital	General Hospital	Clinic	Other
Australia	4	3 (75)	3	0	0	0	3	0	0	0
China	6	5 (83)	0	5	0	0	3	2	0	0
Hong Kong SAR China	10	8 (80)	8	0	0	0	3	5	0	0
India	33	13 (40)	2	12	0	0	10	2	1	0
Japan	20	20 (100)	10	9	0	1	4	16	0	0
South Korea	7	5 (71)	1	2	0	2	5	0	0	0
Malaysia	2	2 (100)	1	0	1	0	2	0	0	0
Myanmar	12	8 (67)	4	4	0	0	7	1	0	0
Pakistan	22	8 (36)	2	4	0	2	6	0	1	1
Philippines	2	2 (100)	1	1	0	0	1	0	1	0
Singapore	9	6 (67)	5	1	0	0	3	2	0	1
Taiwan	11	5 (45)	5	0	0	0	4	0	0	1
Thailand	3	2 (67)	2	0	0	0	2	0	0	0
Total	141	87 (62)	44	38	1	5	53	28	3	3

3.2. Number of patients by age

Among the 87 clinicians, 79 (91%) were aware of the DMD care recommendations [27,28] which had been established as a standard of care. Moreover, 83 clinicians (95%) reported currently managing patients with DMD (between 2011 and 2015) and 4 clinicians (5%) reported managing patients with DMD only before 2011.

Table 2 presents the reported number of patients with DMD, and those treated with steroids, by age group. The number of patients followed-up by the study participants differed depending on the country as well as the age group. In China, 5 neurologists followed-up 1385 patients in total and 853 patients were treated with steroids, which were the highest numbers among the countries that responded to the survey. Moreover, regarding the distribution of followed-up patients in China, more than 80% of the patients were aged 0–9 years, 15% were aged 10–19 years, and only 1% were older than 19 years. In Japan, 1032 patients were followed-up by 20 clinicians; of these patients, 27% were aged 0–9 years, 35% were aged 10–19 years, and 38% were older than 19 years.

3.3. Experience with steroid treatment

Among the 87 clinicians, 77 (89%) had experience administering steroid therapy for DMD, while 70 (80%) were current prescribers (meaning they had prescribed steroids between 2011 and 2015) and 7 (8%) were past prescribers who prescribed steroids before 2011.

There were 10 (11%) clinicians who had never prescribed steroids (3 Japan, 2 Myanmar, 1 Hong Kong, 1 Singapore, 1 Philippines, 1 India, 1 Taiwan). There were several reasons provided for the decision not to prescribe steroids: 6 answered, "I and/or my patient disagree with steroid therapy;" 3 clinicians answered, "I don't know steroid therapy very well;" (both answers were selected by 1 clinician.) and 2 answered, "the patients were not able to walk." When we further probed into the reasons with the follow-up question as to why the 6 clinicians reported that they and/or their patients disagreed with steroid therapy, 3 answered, "because I am concerned about the side-effects" and 3 answered, "because my patient/patient's family was concerned about the side-effects."

3.4. Age at steroid treatment initiation

Clinicians provided several reasons for determining the age at which steroids were initiated: 40 (52%) answered, "when the patient's motor development reached a plateau;" 37 (48%) answered, "when the patient is of a suitable age;" and 5 (6%) supplied both of these reasons.

In response to the open-ended question on steroid initiation age, among the 37 clinicians using age to determine steroid initiation, 22 (60%) considered an appropriate age to be 4–7 years old, 5 (14%) considered ages younger than 4 years old (youngest: 2 years old), and 1 each considered the ages of 5–10 and 6–9 years old. Finally, 2 (5%) clinicians responded that initiation of treatment is appropriate "at diagnosis" or "as early as possible," and 2 (5%) answered "I don't know." Answers were unavailable from 2 clinicians.

3.5. Steroid regimens

Fig. 2 presents the steroid regimens reported by 80 clinicians (70 current steroid prescribers and 10 non-prescribers). Although PSL was used in all the countries surveyed, DFZ was only used in Australia, India, Singapore, and South Korea. In terms of the steroid regimen at initiation among the current prescribers, daily administration of PSL was the most common (median dose:

Table 2
Patients with Duchenne muscular dystrophy, with or without steroid use, followed-up by respondent local experts.

Country	Current follow-up patients (2011–2015)					Current follow-up patients on steroid (2011–2015)				
	Clinicians	Total	0–9 years	10–19 years	>19 years	Clinicians	Total	0–9 years	10–19 years	>19 years
Australia	3	233 (100%)	122 (52%)	111 (48%)	0 (0%)	3	145 (100%)	89 (61%)	56 (39%)	0 (0%)
China	5	1385 (100%)	1157 (84%)	213 (15%)	15 (1%)	5	853 (100%)	693 (81%)	160 (19%)	0 (0%)
Hong Kong SAR China	8	62 (100%)	26 (42%)	26 (42%)	10 (16%)	6	21 (100%)	13 (62%)	7 (33%)	1 (5%)
India	13	494 (100%)	325 (66%)	143 (29%)	26 (5%)	12	322 (100%)	244 (76%)	78 (24%)	0 (0%)
Japan	20	1032 (100%)	276 (27%)	363 (35%)	393 (38%)	14	402 (100%)	167 (41%)	191 (48%)	44 (11%)
South Korea	4	87 (100%)	39 (45%)	34 (39%)	14 (16%)	4	53 (100%)	29 (55%)	20 (38%)	4 (8%)
Malaysia	2	50 (100%)	24 (48%)	23 (46%)	3 (6%)	2	14 (100%)	9 (64%)	5 (36%)	0 (0%)
Myanmar	7	69 (100%)	41 (59%)	23 (33%)	5 (7%)	6	54 (100%)	33 (61%)	16 (30%)	5 (9%)
Pakistan	8	304 (100%)	231 (76%)	72 (24%)	1 (0.3%)	7	145 (100%)	128 (88%)	16 (11%)	1 (1%)
Philippines	1	6 (100%)	5 (83%)	1 (17%)	0 (0%)	1	3 (100%)	2 (67%)	1 (33%)	0 (0%)
Singapore	6	112 (100%)	29 (26%)	58 (52%)	25 (22%)	5	48 (100%)	18 (38%)	28 (58%)	2 (4%)
Taiwan	4	75 (100%)	31 (41%)	34 (45%)	10 (13%)	3	30 (100%)	14 (47%)	15 (50%)	1 (3%)
Thailand	2	45 (100%)	20 (44%)	25 (56%)	0 (0%)	2	35 (100%)	15 (43%)	20 (57%)	0 (0%)
Total	83	3954				70	2125			

0.75 mg/kg/day), followed by PSL every other day, PSL 10 days on 20 days off, DFZ daily (median dose: 0.9 mg/kg/day), PSL 10 days on 10 days off, PSL 2 days/week, and DFZ every other day.

As maintenance therapy, daily administration of PSL was used most commonly (median: 0.725 mg/kg/day), followed by PSL every other day, PSL 10 days on 20 days off, DFZ daily (median: 0.825 mg/kg/day), PSL 2 days/week, DFZ every other day, and PSL 10 days on 10 days off.

3.6. Steroid therapy for non-ambulant patients

Fig. 3 presents the data regarding the use of steroid therapy for non-ambulant patients, as reported by our respondents. We asked the clinicians 3 questions to elucidate their use of steroids for these patients.

(a) "*Usually, do you continue steroid therapy for your patient after loss of walking ability as long as side-effects (for example, bone fracture) are controlled?*"

Among steroid prescribers, 46 (59.7%) answered "Yes," 29 (37.7%) answered "No," and 2 (2.6%) answered "I don't know" to this question. More clinicians in Japan, Singapore, and South Korea tended to continue steroid treatment after the loss of ambulation than those in India and China.

(b) "*Do you cut down the dose when your patient becomes wheelchair bound?*"

Among steroid prescribers, 49 (64%) answered "Yes," 23 (30%) answered "No," and 5 (6%) answered "I don't know."

In most countries, many clinicians tended to reduce the dose after the loss of ambulation, which was different from the practice among the clinicians in Japan.

(c) "*Do you offer steroids routinely to your patient who is wheelchair bound but never had steroids before?*"

Among steroid prescribers, 21 (27%) answered "Yes," 50 (65%) answered "No," and 6 (8%) answered "I don't know." In most countries, few clinicians tended to prescribe steroids for wheelchair-bound patients naïve to steroids.

3.7. Experience of side effects

We enquired about the experience of side effects leading to the withdrawal of steroid therapy by asking clinicians, "*Have you ever been compelled to give up steroid therapy because of the side effect(s)?*" Among steroid prescribers, 47 (61.0%) answered "Yes," 27 (35.0%)

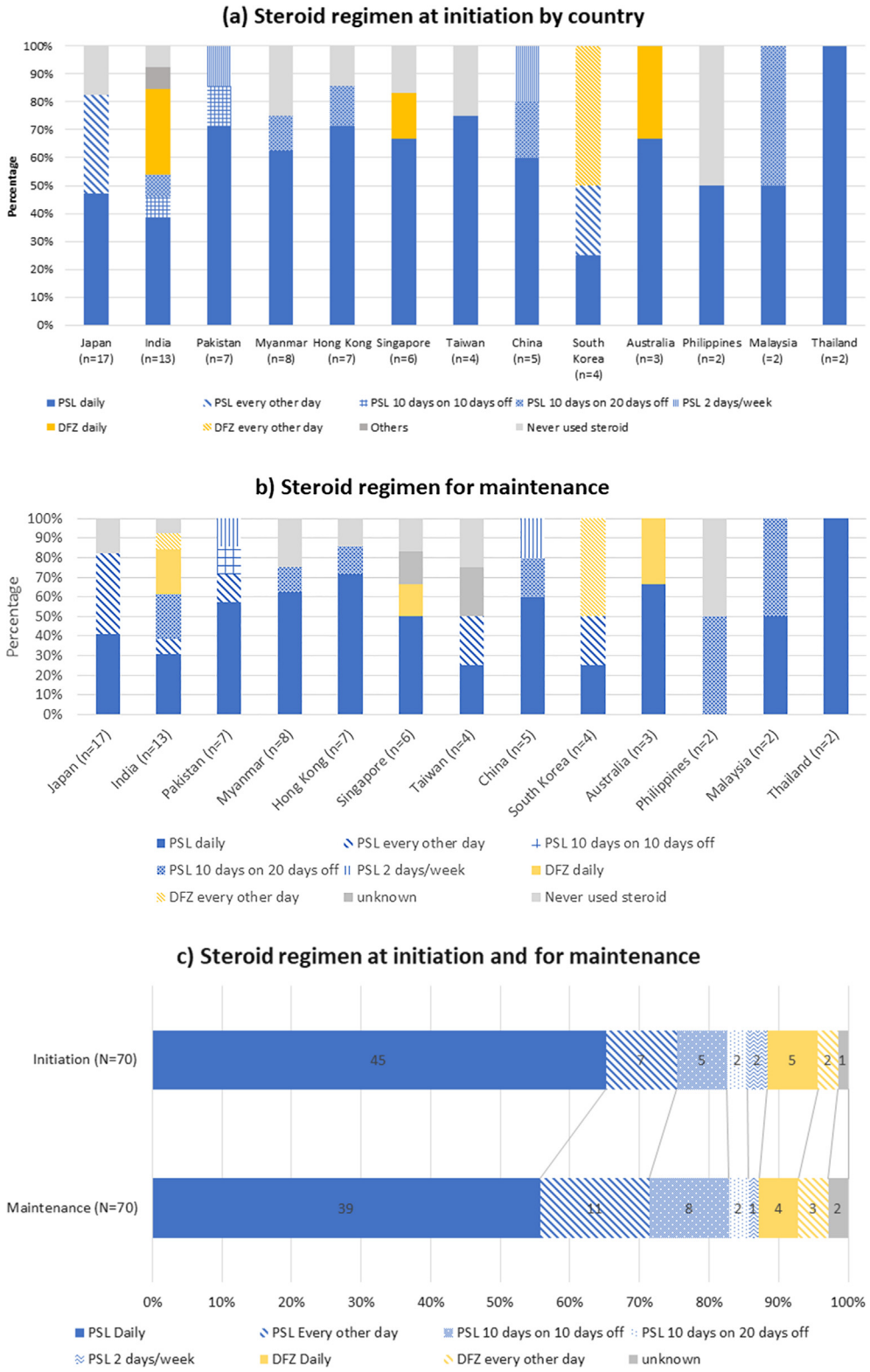

Fig. 2. Steroid regimens used by the clinicians in our survey. a) Steroid regimen at initiation by country. b) Steroid regimen for maintenance by country. c) Steroid regimen at initiation and for maintenance by all clinicians replied. a) Prednisolone and/or prednisone (PSL) was used by clinicians in the all 13 countries, and Deflazacort (DFZ) was used in 4 countries (India, Singapore, South Korea, Australia). Steroid regimen use was inconsistent by country and/or clinician. b) For maintenance, intermittent PSL/DZ regimens were more used in some countries than at initiation. c) Steroid regimens used among 70 clinicians who prescribed Duchenne muscular dystrophy patients with steroids between 2011 and 2015. Daily PSL was most popular at initiation (45/70). Some clinicians tended to switch from daily to alternative regimens (every other day, 10 days on 20 days off) as maintenance therapy.

answered "No," and 3 (3.9%) answered "I don't remember."

Among the side effects that forced the clinicians to withdraw the steroid therapy, obesity was reported most frequently (N = 41; 87%), followed by behavioural changes (N = 18; 38%), bone demineralization (N = 16; 34%), bone fracture (N = 16; 34%), immune suppression (N = 14; 30%), glucose intolerance (N = 13; 28%), hypertension (N = 6; 13%), and others (N = 4; 9%).

3.8. Bone health

Fig. 4 presents details of clinical practices for preserving bone health in the patients using steroids. We assessed the treatments used by clinicians for preserving bone health with 2 questions.

(a) "*Do you assess bone health routinely?*"

Among the 77 steroid prescribers, 47 (61%) conducted routine bone health assessments and 30 (39%) did not. To assess bone health, dual-energy X-ray absorptiometry (DXA) scans were used most commonly, by 38 clinicians (81%), followed by biochemical markers and lateral spine X-rays. Also, more clinicians in Japan, India, Pakistan, Hong Kong, and South Korea than those in other countries used DXA scans, however, that was not statistically significant.

(b) "*Do you use any drugs/supplements as bone protection from steroids?*"

Among steroid prescribers, 57 (74%) prescribed drug (s) and/or supplement(s) for bone protection, and 20 (26%) did not. There was a tendency toward less medication used for bone protection among clinicians in Japan and Myanmar than in India, Pakistan, Hong Kong, Singapore, Taiwan, China, and South Korea.

Regarding drugs and supplements used for bone protection (multiple choice was available), vitamin D was used most commonly, by 50 clinicians (88%), followed by calcium by 45 (79%), bisphosphonate by 18 (32%), and other by 1 (2%). Bisphosphonate was used more frequently (40%) than other drugs or supplements among Japanese clinicians, while calcium and vitamin D were used more frequently in other countries, although that was not statistically significant.

4. Discussion

Currently, increasingly more research papers regarding patients' epidemiology and/or clinical practice in DMD cases have been published from Western countries using a research infrastructure such as a national

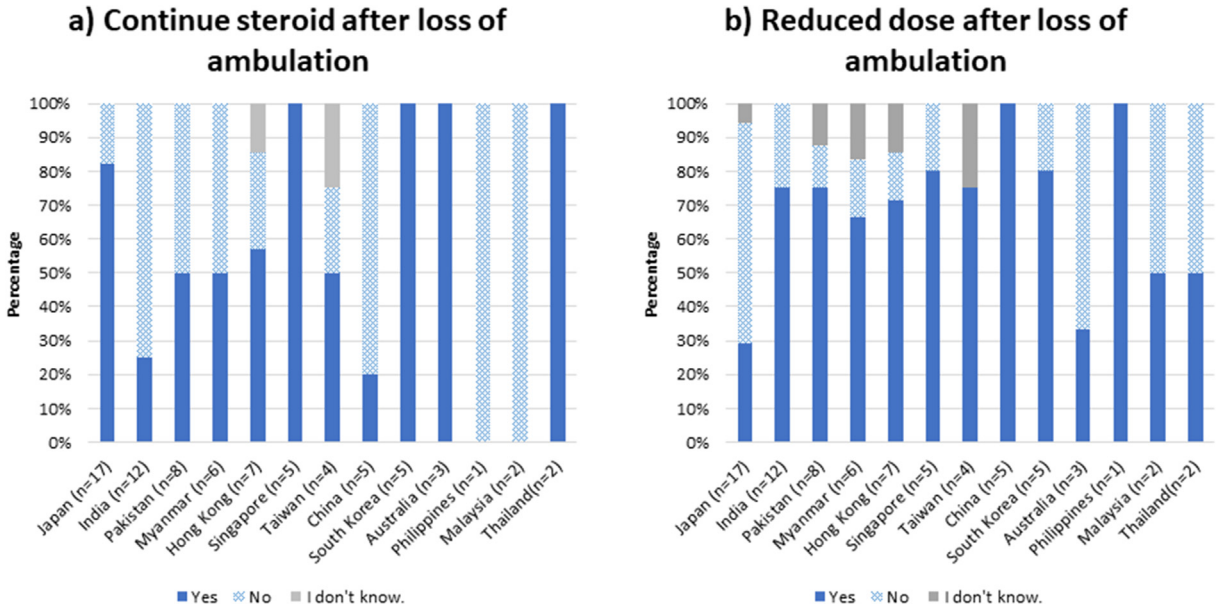

Fig. 3. Steroid therapy in non-ambulant patients. a) Continued steroid treatment after loss of ambulation. b) Reduced steroid dose after loss of ambulation. c) Steroid initiation in non-ambulant patients. a) Over half (46/77, 60%) of the clinicians indicated that they continue steroid treatment after their patients lose ambulation, while 38% (29/77) specified they did not, and 3% (2/77) stated "I don't know". Clinicians in some countries such as Japan, Singapore and South Korea seemed more positive to continue steroid after loss of ambulation. b) Regarding reduced steroid dosage, 64% of the clinicians (49/77) answered that they lower the steroid dosage when the patient loses ambulation, 30% (23/77) indicated they did not, and 6% (5/77) replied "I don't know". Thus, clinician opinions about steroid therapy after loss of ambulation seemed to be different. More than half of responding clinicians in most countries such as India and Pakistan agreed to reduce steroid dose, that was not observed in Japan and Australia. c) Over half of the responding clinicians (65%) disagreed with steroid initiation for non-ambulatory patients. Overall, the clinicians in most countries seemed negative.

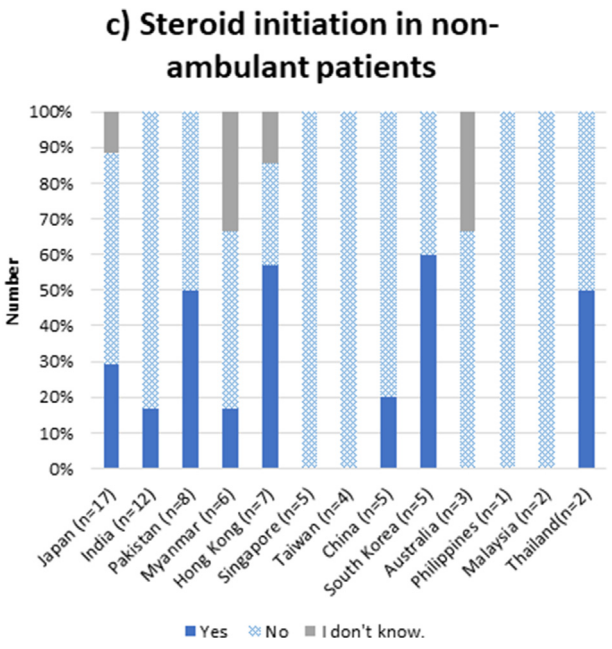

Fig 3. *(continued)*

patient registry. Nonetheless, relevant research evidence is still lacking in Asian and Oceanian countries; also, research infrastructures in rare diseases have been underdeveloped in many of these countries [29].

Accordingly, this study was carried out to investigate the current clinical practice for DMD in Asia and Oceania, in collaboration with the AOMC. The AOMC membership became the target clinician survey population as members are known experts/referral centre heads in the field, and are likely to have the largest clientele to capture DMD cases in their locale. We conducted a survey of clinicians with experience in managing patients with DMD to assess their approach to treatment and management. However, we recognized some limitations because of the specific setting, this study showed that most of the local experts were aware of DMD care recommendations, and prescribed steroids for patients with DMD, Consistent with the suggestions in these guidelines, daily PSL administration was the most frequently used therapy. However, other regimens were also used.

We observed differences in the number of patients with DMD who were followed-up by the respondent local experts in each age group by country. In China, more than 80% of the followed-up patients were aged 0–9 years, which was higher than the percentage in the other countries. Also, more adult patients were followed-up in Japan than in the other countries.

Among the surveyed countries and region, there have been only a few observational studies from Japan [22,30], China [23,24], and Hong Kong [25] which

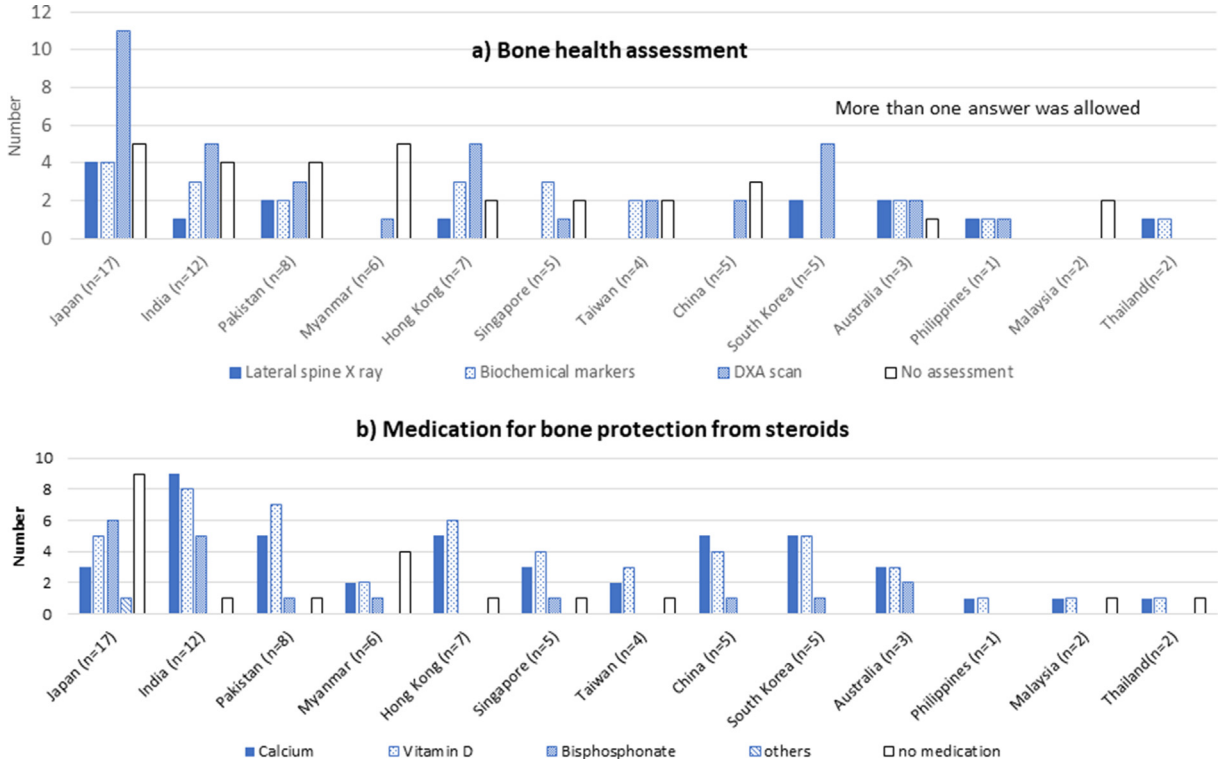

Fig. 4. Approaches to bone health assessment and medication among respondents a) Bone health assessment. b) Medication for bone protection from steroids. a) Routine bone health assessments were carried out by 47 of 77 (61%) clinicians. Dual-energy X-ray absorptiometry (DXA) scans were the most popular (81%), especially in Japan, India, Pakistan, Hong Kong, South Korea. b) Bone health medication was prescribed by 57 of 77 (74%) clinicians. Vitamin D was the most popular (88%), especially in Pakistan, Hong Kong, Singapore, Taiwan. Bone health assessments and treatments were inconsistent by country.

showed detailed epidemiological and/or clinical information in patients with DMD.

So far, two DMD epidemiological studies based on nationwide databases have reported from Japan. First, the Muscular Dystrophy Wards Database which has accumulated inpatients' data with neuromuscular diseases from 27 specialized wards, showed that the mean age of the 733 DMD patients was 30.1 years in 2012 [30]. Among them, 118 were 40 years of age or older (51.0 years of age at the oldest). Second, according to the national patient registry of muscular dystrophy (Remudy) in Japan, 466 out of 583 (80.0%) individuals aged less than 20 years; however, 17 registered individuals were aged over 35 years [22].

From China, two papers have been reported on DMD registry databases at a single centre in East or South China. In the DMD/BMD database at the Children's Hospital of Fudan University in East China, 194 DMD patients and 35 BMD patients were registered with all individuals aged <18 years with 152 individuals (78.4%) aged <10 years [23]. Similarly, in the database of the First Affiliate Hospital of Fuian Medical University, South China, 132 DMD patients were registered with 121 individuals (91.7%) aged <10 years and 11 (8.3%) aged between 10 and 20 years [24]. From Hong Kong, one research paper on DMD/BMD epidemiology which was based on a collaborative study in which all 10 neurology units of the paediatric departments of all the regional hospitals has been published [25]. The age range among the DMD patients (n = 75) was 0.58–34.55 years, with 48 patients (64%) aged >12 years.

Interestingly, the patients' age-profile in Japan, China and Hong-Kong in our study results was similar to those published epidemiological studies [22–25,29].

It also might be possible that the difference of the responding clinicians' specialty had affected the patients' age-profile in our result. As Table 1 shows, the specialty of the clinicians from Australia and Thailand were all paediatrics or child neurology, that might be a reason why no patients aged >19 years were listed.

Taken together, it could be possible that our results may reflect some differences of epidemiology, followed-up system or life expectancy of DMD patients in each country.

The lack of a DMD patients database may contribute to the lack of epidemiology studies from surveyed countries, which might be one of the big differences regarding available background information in rare disease research from Western countries compared to non-Western countries. In fact, according to Xu [31], social support for patients with DMD in China is unsatisfactory and government support has been insufficient to finance research. Therefore, it has been difficult to obtain a precise life expectancy for patients with DMD in China, as has been established in Western countries, because long-term follow-ups are lacking.

Most clinicians participating in this study were aware of the DMD care recommendations published in 2010 [27,28], and prescribed steroids for patients with DMD. However, according to previous studies [22–25], steroid therapy does not appear to be widely used among patients with DMD in Asian countries. In studies based on databases of patients with DMD, the steroid use rate was 26.3% in East China [23], 20.5% in South China [24], 25.3% in Hong Kong [25], and 41.0% in Japan [22]. While, the steroid use rate from our study was 61.6% in China, 33.9% in Hong Kong, and 39.0% in Japan. Comparing aforementioned values with our present survey of clinicians, there is an overall improvement in the clinical steroid use rates and application among the present set of participating clinician experts. However, a caveat is that given the differences in the expert survey target population and sample size, the findings may also relate to the greater awareness of steroid use and practical application for DMD care among clinicians in the participating Asian countries in recent years. Moreover, 10 clinicians (11%) reported that they had never prescribed steroids although 8 of those clinicians were aware of DMD care recommendation, because they and/or their patients objected to steroid therapy due to concerns about side effects (60%), or because they were not familiar with steroid therapy (30%); these values were similar to those in clinical practice in Europe. According to a survey of patients with DMD in Europe, 65.2% of 704 patients with DMD aged ≥9 years had used steroids; of the remaining patients who had not used steroids, 52.8% reported that this was because doctors had not suggested the treatment and 44.2% answered that this was because their parents objected to the treatment [21]. An observational study on the clinical outcomes of DMD across many healthcare settings confirms the benefits of corticosteroid treatment on ambulation, the need for scoliosis surgery, ventilation, and, to a lesser extent, cardiomyopathy [20]. Although earlier steroid initiation is also considered among some clinicians, as previously reported [32], the current care standards recommend commencing corticosteroid use around 4–6 years of age [7,27]. As such, most clinicians consider initiating steroid therapy at a motor development plateau and/or between 4 and 7 years of age. Although PSL was used in all the countries surveyed, DFZ was used by only 8 clinicians in 4 countries (India, Australia, South Korea, and Singapore), which is consistent with previous studies from India [33], Australia [34], and South Korea [35]. However, no studies from Singapore have been previously published. Of note, and based on findings from this present AOMC survey, DFZ has been available in South Korea and India, and was also previously available in Pakistan. A regimen of daily PSL administration was the most popular regimen among clinicians, although some clinicians tended to switch from a daily to an alter-

native regimen (every other day or 10 days on 20 days off) for maintenance. Our results also replicated the variation in steroid regimens that was previously reported in similar studies from the US, Canada, Western Europe and Japan [15–19].

In the present study, 61% of the clinicians who had experience prescribing steroid therapy for DMD cases had been compelled to stop steroid therapy because of the side effects. Obesity was the most commonly reported side effect that resulted in steroid therapy withdrawal, which is consistent with a previous study from the United States [36].

In the patients who used steroids while ambulant, many experts have reported continued medication after the loss of ambulation with the goal of preserving upper limb strength, reducing the progression of scoliosis, and delaying a decline in respiratory and cardiac functions [7,27]. However, our present survey results indicate that there is no apparent standard steroid therapy for non-ambulant patients. In particular, most clinicians did not initiate steroid treatment for non-ambulant patients, which could be due to the lack of evidence for the effectiveness of initiating steroid treatment in preventing scoliosis or in stabilizing cardiac or respiratory function in these patients [7,27].

The 2010 DMD care recommendations suggest the use of serum tests (calcium, phosphate, alkaline phosphatase, and 25-OH vitamin D levels) and urine tests (calcium, sodium, and creatinine levels) to assess bone health [31]. Both DXA scans and spine radiographs are also indicated for bone imaging assessment purposes [31]. In the 2018 care considerations, spine radiographs should be prioritized over DXA in view of the need to detect the earliest signs of bone fragility [7]. Our results suggest that there is an inconsistency in the bone health assessments among the countries surveyed; DXA scans were used more frequently in Japan, India, China Hong Kong SAR, and South Korea, while they were not used in Malaysia or Thailand. Moreover, lateral spine X-rays were not used in Myanmar, Singapore, Taiwan, China, or Malaysia, and biochemical markers were not used in Myanmar, China, South Korea, and Malaysia. These differences might reflect the differences in availability or accessibility of bone imaging among the countries. Further research is needed to analyse the implications of these inconsistencies in bone health assessments.

In addition, we observed differences in clinical practice habits regarding medications used for bone protection. The current guidelines list vitamin D, calcium, and bisphosphonate (intravenous or oral) as possible interventions for preserving bone health [31]. However, a 2017 Cochrane review [37] reported that there was no evidence from randomized clinical trials to guide the use of treatments to prevent or treat osteoporosis, and to prevent fragility fractures in patients with DMD receiving corticosteroids. Interestingly, clinical practice habits among Japanese clinicians were divided, with half of the clinicians choosing not to prescribe medication for bone health, while those who did prescribe medication more frequently used bisphosphonate than they did Vitamin D or calcium. Among Japanese clinicians, the age of patients who had been prescribed bone health intervention(s) was similar to that of those who were not prescribed interventions, although this was an observational assumption.

Our present study has several strengths, including that it is the first international epidemiological study of expert-driven clinical practice relating to DMD in 13 countries and regions in Asia and Oceania, while previous international epidemiological studies have been conducted mainly in Western countries [15,16,20,21,38]. The TREAT-NMD study facilitated the establishment of standardized national registries of patients with DMD in multiple countries worldwide via the use of a standardized mandatory dataset collected by each registry. Registries involve much wider population cohorts and may demonstrate country-specific differences usually not captured by natural history (observational) clinical studies [20]. Among the 13 countries surveyed, a DMD registry had been established in 5 countries and regions (Australia, China, China Hong Kong SAR, India, and Japan) as of April 2017, in collaboration with TREAT-NMD [39]. Although multi-national characteristics of patients with DMD/BMD have been described in several studies from Asian countries, epidemiological data, natural history, and information about care practice in Asia and Oceania are still lacking. Therefore, we believe that our study provides a snapshot which helps to reveal current clinical practices for DMD in these countries in which national registries of patients with DMD have not yet been established.

Nonetheless, we also recognize that our present study is subject to some limitations. Although the total response rate was 62%, the number of study participants from each country was small. In addition, there are no available data on the total number of neurologists or child neurologists in these countries. Therefore, there is a potential selection bias, which may mean that our results may not accurately reflect DMD clinical practice in these countries. However, we believe our study likely offers insight into the care provided by the clinicians nominated by an executive committee of the AOMC that has been dedicated to ensure an international collaboration for developing research and treatment in patients with neuromuscular diseases in Asia and Oceania.

Further research is required to elucidate the epidemiology, natural history, and care practice for DMD in Asia and Oceania. In particular, a full understanding of the epidemiology and natural history of DMD requires the establishment of a nationwide patient registry and accumulation of patient data. However, the establishment and maintenance of a patient registry will

require support from local health authorities, clinicians, and patient support groups [23,25,30].

5. Conclusions

Our results from an international survey of clinicians increase the existing knowledge of the current clinical practice for DMD, as reported by local experts in Asia and Oceania. We observed that most of the clinicians were aware of DMD care recommendations, and prescribed steroids for patients with DMD. As suggested by the guidelines, daily PSL administration was the most frequently used therapy. However, other regimens were also used. In contrast, there were inconsistencies among the clinicians' strategies for steroid therapy in non-ambulant patients and for bone health medication, both of which continue to be controversial worldwide.

We suggest that it is important to expand the registries of patients with DMD in Asia and Oceania, and to accumulate real-world longitudinal patient data. These strategies will aid the study of the epidemiology and natural history of DMD and could improve treatment and care for patients with DMD worldwide.

6. Declarations

6.1. Ethics approval and consent to participate

A draft questionnaire was reviewed by AOMC executive board members. Approval for this study was granted by the ethics committee of the National Center of Neurology and Psychiatry (A2015-031). Participation in this survey was voluntary, and a response to the questionnaire was regarded as an agreement to participate. Participants were not compensated for their participation.

6.2. Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

6.5. Authors' contributions

FT designed the study and analysis, collected, analysed and interpreted data, and drafted the manuscript. HN, NY and HK contributed to study design, the development of the clinician survey and edited the manuscript. RR, AK, AB, CD, KG, YJ, DK, SK, DS, KW, JC, SC, SK, and OO contributed to the recruitment of study participants, and reviewed and edited the manuscript. IN contributed to the study design, recruitment of study participants, and reviewed and edited the manuscript. IN and ST contributed to the study design and reviewed and edited the manuscript. All authors read and approved the final manuscript.

Acknowledgements

We gratefully acknowledge the cooperation of the AOMC executive committee as of 2015. We also appreciate the help of Ms. Mikiko Shigemori with the survey. We thank Editage (http://www.editage.jp/) for English language editing. Finally, we are very grateful to all the clinicians who took the time to respond to the questionnaire.

References

[1] Mendell JR, Shilling C, Leslie ND, Flanigan KM, al-Dahhak R, Gastier-Foster J, et al. Evidence-based path to newborn screening for Duchenne muscular dystrophy. Ann Neurol 2012;71:304–13.
[2] Darras BT, Urion DK, Ghosh PS. Dystrophinopathies. In: Adam MP, Ardinger HH, Pagon RA, Wallace SE, Bean LJH, Stephens K, et al. editors. GeneReviews®. Seattle: University of Washington; 1993–2019. https://www.ncbi.nlm.nih.gov/books/NBK1119/. Accessed 20 February 2019.
[3] Leung DG, Wagner KR. Therapeutic advances in muscular dystrophy. Ann Neurol 2013;74:404–11.
[4] Ryder S, Leadley RM, Armstrong N, Westwood M, de Kock S, Butt T, et al. The burden, epidemiology, costs and treatment for Duchenne muscular dystrophy: an evidence review. Orphanet J Rare Dis 2017;12:79.
[5] Moxley 3rd RT, Ashwal S, Pandya S, Connolly A, Florence J, Mathews K, et al. Practice parameter: corticosteroid treatment of Duchenne dystrophy: report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. Neurology 2005;64:13–20.
[6] Moxley 3rd RT, Pandya S, Ciafaloni E, Fox DJ, Campbell K. Change in natural history of Duchenne muscular dystrophy with long-term corticosteroid treatment: implications for management. J Child Neurol 2010;25:1116–29.
[7] Birnkrant DJ, Bushby K, Bann CM, Apkon SD, Blackwell A, Brumbaugh D, et al. Diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis, and neuromuscular, rehabilitation, endocrine, and gastrointestinal and nutritional management. Lancet Neurol 2018;17:251–67.
[8] Manzur AY, Kuntzer T, Pike M, Swan A. Glucocorticoid corticosteroids for Duchenne muscular dystrophy. Cochrane Database Syst Rev 2008::CD003725.
[9] Escolar DM, Hache LP, Clemens PR, Cnaan A, McDonald CM, Viswanathan V, et al. Randomized, blinded trial of weekend vs daily prednisone in Duchenne muscular dystrophy. Neurology 2011;77:444–52.
[10] Brooke MH. Clinical investigation of Duchenne muscular dystrophy. Arch Neurol 1987;44:812–7.

[11] Fenichel GM, Mendell JR, Moxley 3rd RT, Griggs RC, Brooke MH, Miller JP, et al. A comparison of daily and alternate-day prednisone therapy in the treatment of Duchenne muscular dystrophy. Arch Neurol 1991;48:575–9.
[12] Beenakker EA, Fock JM, Van Tol MJ, Maurits NM, Koopman HM, Brouwer OF, et al. Intermittent prednisone therapy in Duchenne muscular dystrophy: a randomized controlled trial. Arch Neurol 2005;62:128–32.
[13] Sansome A, Royston P, Dubowitz V. Steroids in Duchenne muscular dystrophy; Pilot study of a new low-dosage schedule. Neuromuscular Disord 1993;3:567–9.
[14] Gloss D, Moxley 3rd RT, Ashwal S, Oskoui M. Practice guideline update summary: corticosteroid treatment of Duchenne muscular dystrophy: Report of the Guideline Development Subcommittee of the American Academy of Neurology. Neurology 2016;86:465–72.
[15] Griggs RC, Herr BE, Reha A, Elfring G, Atkinson L, Cwik V, et al. Corticosteroids in Duchenne muscular dystrophy: major variations in practice. Muscle Nerve 2013;48:27–31.
[16] Landfeldt E, Lindgren P, Bell CF, Schmitt C, Guglieri M, Straub V, et al. Compliance to care guidelines for Duchenne muscular dystrophy. J Neuromuscular Dis 2015;2:63–72.
[17] van den Bergen JC, Ginjaar HB, van Essen AJ, Pangalila R, de Groot IJ, Wijkstra PJ, et al. Forty-five years of Duchenne muscular dystrophy in The Netherlands. J Neuromuscul Dis 2014;1:99–109.
[18] McMillan HJ, Campbell C, Mah JK, Canadian Paediatric Neuromuscular Group. Duchenne muscular dystrophy: Canadian paediatric neuromuscular physicians survey. Can J Neurol Sci 2010;37:195–205.
[19] Takeuchi F, Komaki H, Nakamura H, Yonemoto N, Kashiwabara K, Kimura E, et al. Trends in steroid therapy for Duchenne muscular dystrophy in Japan. Muscle Nerve 2016;54:673–80.
[20] Koeks Z, Bladen CL, Salgado D, van Zwet E, Pogoryelova O, McMacken G, et al. Clinical outcomes in Duchenne muscular dystrophy: a study of 5345 patients from the TREAT-NMD DMD global database. J Neuromuscul Dis 2017;4:293–306.
[21] Vry J, Gramsch K, Rodger S, Thompson R, Steffensen BF, Rahbek J, et al. European cross-sectional survey of current care practices for Duchenne muscular dystrophy reveals regional and age-dependent differences. J Neuromuscul Dis 2016;3:517–27.
[22] Nakamura H, Kimura E, Mori-Yoshimura M, Komaki H, Matsuda Y, Goto K, et al. Characteristics of Japanese Duchenne and Becker muscular dystrophy patients in a novel Japanese national registry of muscular dystrophy (Remudy). Orphanet J Rare Dis 2013;8:60.
[23] Li X, Zhao L, Zhou S, Hu C, Shi Y, Shi W, et al. A comprehensive database of Duchenne and Becker muscular dystrophy patients (0–18 years old) in East China. Orphanet J Rare Dis 2015;10:5.
[24] Wang DN, Wang ZQ, Yan L, He J, Lin MT, Chen WJ, et al. Clinical and mutational characteristics of Duchenne muscular dystrophy patients based on a comprehensive database in South China. Neuromuscul Disord 2017;27:715–22.
[25] Chan SHS, Lo IFM, Cherk SWW, Cheng WW, Fung ELW, Yeung WL, et al. Prevalence and characteristics of chinese patients With Duchenne and Becker muscular dystrophy: a territory wide collaborative study in Hong Kong. Child Neurol Open 2015;2 2329048X15585345.
[26] Shimizu R, Ogata K, Tamaura A, Kimura E, Ohata M, Takeshita E, et al. Clinical trial network for the promotion of clinical research for rare diseases in Japan: muscular dystrophy clinical trial network. BMC Health Serv Res 2016;16:241.
[27] Bushby K, Finkel R, Birnkrant DJ, Case LE, Clemens PR, Cripe L, et al. Diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis, and pharmacological and psychosocial management. Lancet Neurol 2010;9:77–93.
[28] Bushby K, Finkel R, Birnkrant DJ, Case LE, Clemens PR, Cripe L, et al. Diagnosis and management of Duchenne muscular dystrophy, part 2: implementation of multidisciplinary care. Lancet Neurol 2010;9:177–89.
[29] Song P, Gao J, Inagaki Y, Kokudo N, Tang W. Intractable and rare diseases research in Asia. Biosci Trends 2012;6:48–51.
[30] Saito T, Kawai M, Kimura E, Ogata K, Takahashi T, Kobayashi M, et al. Study of Duchenne muscular dystrophy long-term survivors aged 40 years and older living in specialized institutions in Japan. Neuromuscul Disord 2017;27:107–14.
[31] Xu EX. Professor Shi-Wen Wu: One City, One Doctor-building up the national DMD registry network. Ann Transl Med 2015;3:204.
[32] Merlini L, Gennari M, Malaspina E, Cecconi I, Armaroli A, Gnudi S, et al. Early corticosteroid treatment in 4 Duchenne muscular dystrophy patients: 14-year follow-up. Muscle Nerve 2012;45:796–802.
[33] Petnikota H, Madhuri V, Gangadharan S, Agarwal I, Antonisamy B. Retrospective cohort study comparing the efficacy of prednisolone and deflazacort in children with muscular dystrophy: a 6 years' experience in a South Indian teaching hospital. Indian J Orthop 2016;50:551–7.
[34] Davidson ZE, Ryan MM, Kornberg AJ, Sinclair K, Cairns A, Walker KZ, et al. Observations of body mass index in Duchenne muscular dystrophy: a longitudinal study. Eur J Clin Nutr 2014;68:892–7.
[35] Jung IY, Chae JH, Park SK, Kim JH, Kim JY, Kim SJ, et al. The correlation analysis of functional factors and age with duchenne muscular dystrophy. Ann Rehabil Med 2012;36:22–32.
[36] Matthews DJ, James KA, Miller LA, Pandya S, Campbell KA, Ciafaloni E, et al. Use of corticosteroids in a population-based cohort of boys with duchenne and becker muscular dystrophy. J Child Neurol 2010;25:1319–24.
[37] Bell JM, Shields MD, Watters J, Hamilton A, Beringer T, Elliott M, et al. Interventions to prevent and treat corticosteroid-induced osteoporosis and prevent osteoporotic fractures in Duchenne muscular dystrophy. Cochrane Database Syst Rev 2017;1:CD010899.
[38] Rodger S, Woods KL, Bladen CL, Stringer A, Vry J, Gramsch K, et al. Adult care for Duchenne muscular dystrophy in the UK. J Neurol 2015;262:629–41.
[39] TREAT-NMD: http://www.treat-nmd.eu/dmd/patient-registries/dmd/. Accessed 20 February 2019.

Author/s:
Takeuchi, F; Nakamura, H; Yonemoto, N; Komaki, H; Rosales, RL; Kornberg, AJ; Bretag, AH; Dejthevaporn, C; Goh, KJ; Jong, Y-J; Kim, D-S; Khadilkar, SV; Shen, D; Wong, KT; Chai, J; Chan, SH-S; Khan, S; Ohnmar, O; Nishino, I; Takeda, S; Nonaka, I

Title:
Clinical practice with steroid therapy for Duchenne muscular dystrophy: An expert survey in Asia and Oceania

Date:
2020-03-01

Citation:
Takeuchi, F., Nakamura, H., Yonemoto, N., Komaki, H., Rosales, R. L., Kornberg, A. J., Bretag, A. H., Dejthevaporn, C., Goh, K. J., Jong, Y. -J., Kim, D. -S., Khadilkar, S. V., Shen, D., Wong, K. T., Chai, J., Chan, S. H. -S., Khan, S., Ohnmar, O., Nishino, I. ,... Nonaka, I. (2020). Clinical practice with steroid therapy for Duchenne muscular dystrophy: An expert survey in Asia and Oceania. BRAIN & DEVELOPMENT, 42 (3), pp.277-288. https://doi.org/10.1016/j.braindev.2019.12.005.