Research on dose optimization from the aspect of clinical development and real-world use

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Abstract

The determination of drug dosage is one of the important aspects for the effective and safe usage of pharmaceuticals. Generally, the dosage of pharmaceuticals is determined through the process of clinical development and approval review based on clinical trial results; however, the information obtained from clinical trials before approval is limited. Some pharmaceutical products are used at doses lower than those approved for post-marketing use. The aim of this study was to examine measures to optimize the dosage of pharmaceuticals from the aspect of clinical development and real-world use.

In Research 1, we investigated the actual situate of lower dose prescription in post-marketing clinical use of pharmaceuticals, approved in Japan between 2005 and 2014, based on the medical information databases. Products whose daily dose was lower than the approved dose in ≥ 30% prescriptions were defined here as "lower-dose prescription drugs," and factors that influencing "lower-dose prescription drugs" were explored from the perspective of Anatomical Therapeutic Chemical (ATC) classification, detailed statement of the approved dosage, clinical data package, and post-marketing requirement. We identified 27 "lower-dose prescription drugs" out of 113 products investigated. The results of the multivariate analysis revealed that "antineoplastic agents," "maintenance dose different from the initial dose," and "upward/downward dose adjustment" significantly associated with "lower-dose prescription drugs" ($p < 0.05$).

In Research 2, we investigated the relationship between the proportions of patients who withdrew from the study or whose medication was discontinued, reduced or suspended due to adverse effects (AEs) and of elderly patients to those who were expose to the approved dose range in the pivotal studies, and "lower-dose prescription drugs."

The proportions of patients whose medication was discontinued, and that of patients whose medication was reduced or suspended were both significantly higher for “lower-dose prescription drugs” than for no “lower-dose prescription drugs” ($p < 0.05$).

The present study highlighted prescriptions at doses lower than the approved dose in the actual post-marketing scenario. The factors related to the ATC classification and the detailed statement of the approved dosage significantly influenced the occurrence of “lower-dose prescription drugs”, whereas the factors related to clinical data package and post-marketing requirements did not. This shows a limitation in predicting lower dose prescription in various actual post-marketing situations from the results of clinical trials before approval, and also a possibility that the approved dose may not be identical to the optimal dose after marketing. The proportion of patients whose medication was discontinued, reduced or suspended due to AEs were higher in “lower-dose prescription drugs” than in no “lower-dose prescription drugs. This result suggests a possibility of identifying products that should be actively monitored for clinical use in post-marketing, even though the optimal dose was not identified by the time of approval.

Optimized dose should be indicated in the product label to ensure that anyone can use the drug at the optimal dose. Clinically used dosage in the post-marketing phase of a drug should be monitored, and it is important to search the optimized dosage, which is applicable to a greater number of patients without causing lack of efficacy. The Real-World Data (RWD) would allow us to identify patient backgrounds with lower dose prescriptions and plan post-marketing clinical trials to clarify benefit/risk balance using lower dose for those specific populations, if necessary. We believe that the utilization of RWD would help lead to a prompt delivery of information on the optimized dose for each pharmaceutical product.

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Abbreviations

AD	approved dose
AEs	Adverse Events
AID	approved initial dose
AMD	approved maintenance dose
ATC	Anatomical Therapeutic Chemical
CI	confidence interval
CTD	Common Technical Document
DDD	Defined daily dose
DPC/PDPS	Diagnosis Procedure Combination/Per-Diem Payment System
DSP	dose for special populations
IDSP	initial dose for special populations
MDSP	Maintenance dose for special population
MDV	Medical Data Vision Co., LTD.
MTD	maximum tolerated dose
NMEs	new molecular entities
PRO	Patient-Reported Outcome
PRO-CTCAE	Patient-Reported Outcomes version of Common Terminology Criteria for Adverse Event
RWD	Real-World Data
WHO	World Health Organization

1 Introduction

The determination of drug dosage is one of the important aspects for the effective and safe usage of pharmaceuticals. Generally, the dosage and dosage regimen are decided through the process of clinical development and approval review based on the results of clinical trials. In phase I studies, clinical exposure and tolerability are examined using several doses of a drug in healthy adults and in phase II studies, dose–response relationships are evaluated in a small number of patients, and based on the information obtained, the recommended dose or dose range of the drug is proposed. In phase III studies, the efficacy and safety of the recommended dose are confirmed.

In clinical trials for marketing authorization, there are several restrictions such as exclusion of patients with complications and concomitant medications, and the information obtained from such clinical trials is limited. After marketing, the use of drug is expanded to patients who do not meet clinical trial eligibility criteria, as well as the dose is adjusted according to the condition of individual patients. Thereby, the approved dosage might not be optimal for actual conditions of post-marketing use.

It has been reported that the approved dose of approximately 20% of the new molecular entities (NMEs) in the United States between 1980 and 1999 was changed in the post-marketing phase and that the change to a lower dose due to safety issues accounted for approximately 80% of the overall changes [1]. Defined daily dose (DDD), an average daily dose for adults in the primary indication defined by the World Health Organization (WHO), was changed in the post-marketing phase for 115 products between 1989 and 2000, and approximately 60% of them indicated a change to a lower dose [2]. It has been reported that although a lower dose prescription is often recommended for the elderly population and for reducing side effects [3-6], clinical evidence on using such a

low dose is not reflected in the product label (package insert), even if it is published in medical journals [7-8].

To the best of our knowledge, the actual situation of post-marketing prescription of specific products has not been fully investigated so far. Some studies have reported that, in the clinical development process, phase III trials are often performed using doses close to the maximum tolerated dose (MTD) to focus on the efficacy, and the lower doses of a drug are not sufficiently examined [1, 6, 9]. However, there is no evidence supporting the fact that this is the cause of lower dose prescription in the post-marketing phase.

The aim of this study was to examine measures to optimize the dosage of pharmaceuticals. With this end in view, first, we determined the actual state of lower dose prescriptions for post-marketing clinical use of pharmaceuticals and investigated the factors that might lead to prescriptions of drugs at a lower dose from the viewpoints of Anatomical Therapeutic Chemical (ATC) classification, detailed statement of the approved dosage, clinical data package, and post-marketing requirement (Research 1). Second, we investigated the relationship between the proportion of patients whose medication was discontinued or dosage was reduced due to safety issues in pivotal studies and lower-dose prescriptions in the post-marketing clinical use (Research 2).

2 Research 1 (Lower dose prescriptions in the post-marketing situation and the influencing factors thereon)

2.1 Objectives

The aim of Research 1 was to reveal the actual state of lower dose prescriptions in post-marketing clinical use of pharmaceuticals and to investigate the factors that might lead to prescriptions of drugs at a lower dose. We investigated the actual situation of lower-dose prescriptions by comparing the frequency distribution of the daily dose of each pharmaceutical product using the medical information databases and identified the products for which some prescriptions presented deviation toward lower dose from the approved dosage, and these were termed “lower-dose prescription drugs.”

2.2 Materials and methods

2.2.1 Drugs examined

Information on the daily dose of 342 pharmaceutical products approved as NMEs in Japan between January 1, 2005 and December 31, 2014 was collected. From the medical information databases we used, only prescription data of daily dose were available; whereas background information for individual patients such as height, weight, and complications was not available, and therefore, we could not correlate them with the prescription data. Therefore, we set inclusion and exclusion criteria to identify pharmaceutical products to be investigated using the medical information databases. The inclusion criteria were as follows: 1) drugs administered orally, 2) drugs indicated for adults, and 3) drugs with the same daily dose for different indications (the daily dose does not differ depending on the indication). The exclusion criteria were as follows: 1) combination drugs, pro re nata (as needed) drugs, and drugs not covered by insurance, 2)

drugs with a dosage based on body weight or body surface area, and 3) clinical trials for efficacy and safety not conducted before approval.

2.2.2 Data sources

In the first survey, we used the medical information databases of Medical the Data Vision Co., LTD. (MDV; Tokyo, Japan) and JammNet Co., LTD. (Tokyo, Japan). The database of MDV contains health claim data and administrative data of hospitals in which the payment was made based on the Diagnosis Procedure Combination/Per-Diem Payment System (DPC/PDPS). The database of JammNet contains medical receipt information from health insurance societies in Japan. We investigated the daily dose of the products prescribed for adults (≥ 15 years old at the time of prescription) between January 1 and December 31, 2015. During the survey period, data from approximately 12.65 million individual patients (12.2% < 15 years old, 45.8% ≥ 15 < 65 years old, and 42.0% ≥ 65 years old) from 225 medical institutions (hospitals only) were included in the database of MDV and data from approximately 630,000 patients (20.3% < 15 years old, 64.0% ≥ 15 < 65 years old, and 15.7% ≥ 65 years old) from 72,156 medical institutions (6,544 hospitals and 65,612 clinics) were included in the database of JammNet. Although the database of MDV has a large amount of data equivalent to one in seven Japanese citizens, considering the fact that information from clinics is not included and that the age composition differs between the two databases, we also utilized the database of JammNet to gain further insights on prescription trends.

In the second investigation, we extracted information pertaining to products such as ATC classification, detailed statement of the approved dosage, clinical data package, and post-marketing requirement from the publications, including product label, approval

submission dossier (Common Technical Document: CTD), and review report.

2.2.3 Definition of "lower-dose prescription drugs"

We counted the prescriptions in each category of daily dose and calculated the percentage to the total number of prescriptions in the two databases. The categories were as follows (Table1):

1) In Japanese product labels, approved dose described in the section "Dosage and administration" are clearly distinguished from dose information for special populations described in the section "Precautions concerning dosage and administration" and "Precautions concerning patients with specific backgrounds" [10]; therefore, the dose for special populations was compiled separately from the approved doses, if any.
2) The initial dose and titration dose were defined as "initial dose" and compiled separately from the maintenance dose because the initial dose is prescribed only for a limited period before reaching the maintenance dose.
3) If there was a separate statement on the initial dose for special populations in the product label, it was compiled as a different category.
4) Categories with doses less than the minimum dose and exceeding the maximum dose mentioned in points 1 to 3 above were also set respectively, if any.

Products whose percentage of prescriptions corresponding to the category of doses lower than the approved dose, or the approved maintenance dose if the initial dose is set, was ≥ 30% in the database of either MDV or JammNet were defined as "lower-dose prescription drugs". In addition, in order to perceive the distribution of the daily dose for each drug, we calculated the median and quartile points using the database of MDV.

Table 1. Categories of daily dose and their definitions

Category of daily dose	Definition	Section in product label
Approved dose (AD)	Daily dose for adults	"6. DOSAGE AND ADMINISTRATION"
Approved initial dose (AID)	Daily dose in initial and titration period	
Approved maintenance dose (AMD)	Daily dose excluding AID	
Dose for special populations (DSP)	Daily dose for special populations	"7. PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION" "9. PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS"
initial dose for special populations (IDSP)	Daily dose for special populations in initial and titration period	
Maintenance dose for special population (MDSP)	Daily dose for special populations excluding IDSP	

2.2.4 Factors examined

To explore the factors influencing "lower-dose prescription drugs," we extracted information pertaining to ATC classification, detailed statement of the approved dosage, clinical data package, and post-marketing requirement. Eleven factors investigated in the present research were as follows:

1) ATC classification. Using the ATC code, products of "L01 antineoplastic agents" were classified as antineoplastic agents, because they have characteristics considerably different from those of other pharmaceutical products in terms of dosage selection in the clinical development process [11].

2) Detailed statement of the approved dosage. Three factors, "dose in range," "maintenance dose different from the initial dose," and "upward/downward dose adjustment," were investigated. "Dose in range" indicates that the approved dosage is defined with a certain width. For instance, products whose dosage are

described as “X mg or Y mg depending on the condition” or “X mg in the usual case and Y mg in case of inadequate effect” were classified as “dose in range.” With respect to “upward/downward dose adjustment”, products with descriptions such as “dose may be adjusted” or “dose may be reduced” according to the patient’s condition were classified as “upward/downward dose adjustment.”

3) Clinical data package. Six factors, “orphan drugs,” “bridging strategy or multi-regional clinical trial,” “approved before 2009,” “dose finding study,” “lower dose in pivotal study,” and “safety concern,” were investigated. In “approved before 2010,” products were divided into 2 groups based on their initial approval year. “Dose finding study” was defined as a study to examine efficacy and safety comparing two or more fixed dosages. For instance, products for which phase II clinical trials using only one dose of MTD or flexible dose were conducted were not classified as “dose finding study.” In “lower dose in pivotal study”, a pivotal study basically means phase III clinical trial, and exceptionally concerning the products such as antineoplastic agents for which phase III clinical trials are not conducted before approval, it means the latest phase clinical trial. When more than one phase III clinical trials were conducted, the products for which doses lower than the approved dose was examined in any of the studies were classified as “lower dose in pivotal study.” “Safety concern” was defined as the case for which adverse effects were taken into account in the recommended dose selection of a product, and the products with descriptions concerning adverse effects in the dose selection in the review reports or CTDs were classified as “safety concern.”

4) Post-marketing requirement. Products with the requirement for conducting post-marketing clinical studies or all case surveys were defined as “approval

conditions.”

2.2.5 Analyses

We conducted univariate and multivariate logistic regression analyses using “lower-dose prescription drugs” as a response variable and the 11 factors mentioned above as exploratory variables. A significant association was defined at p value < 0.1 in the univariate analysis, and all the associated variables were incorporated into the multivariate model; when a strong association (Cramér's V > 0.5) was identified between the selected explanatory variables in the univariate analysis, only one of the factors was selected to be included in the multivariate analysis. In the multivariate analysis, a statistically significant association was defined at p value < 0.05. The analyses were performed using StatsDirect (StatsDirect LTD., Cheshire, UK).

2.3 Result

2.3.1 Drugs examined

From a total of 342 pharmaceutical products approved as NMEs in Japan between 2005 and 2014, we selected 140 products that fulfilled all the inclusion criteria. After excluding 27 products, a dataset of 113 products was created (Fig 1 and Table 2).

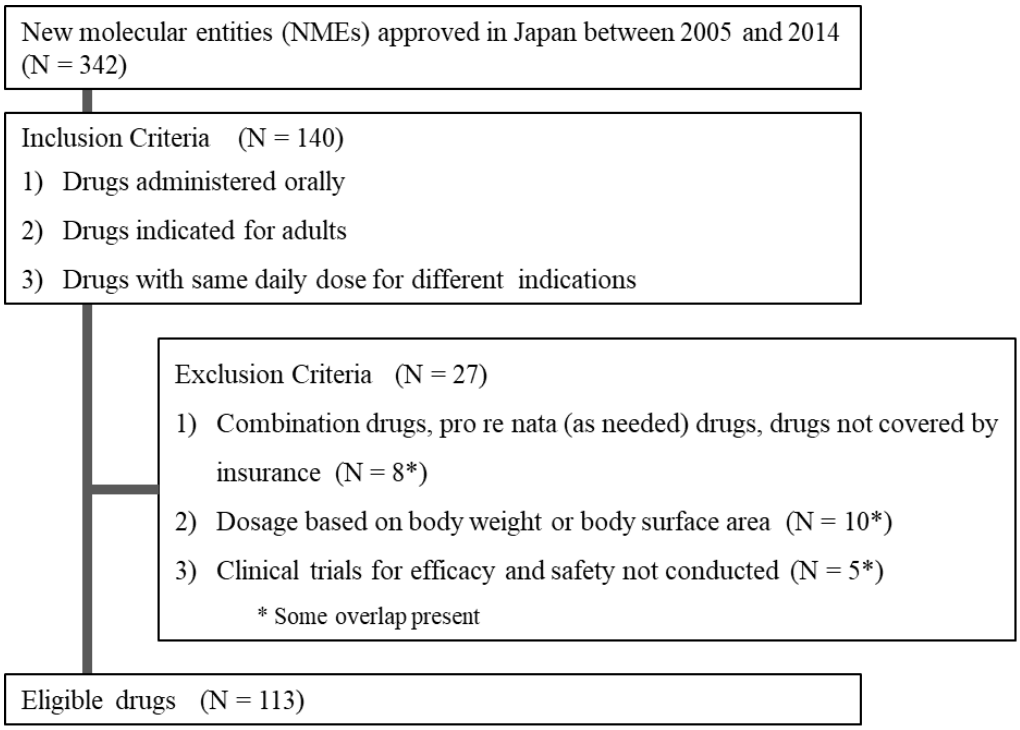


Fig 1. Flowchart representing the selection of drugs to be investigated.

Table 2. Dataset of factors related to the ATC classification, detailed statement of the approved dosage, clinical data package, and post-marketing requirement for each eligible drug.

No.	Drug	F0	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11
1	Abiraterone	0	0	0	0	0	0	0	0	1	0	0	0
2	Acamprosate	0	0	0	0	0	0	0	0	1	0	0	0
3	Acotiamide	0	0	0	0	0	0	0	0	1	0	0	0
4	Afatinib	1	1	1	0	0	0	1	0	0	0	1	0
5	Alectinib	0	1	0	0	0	1	0	0	0	0	0	1
6	Aliskiren	0	0	1	0	0	0	0	1	1	1	0	0
7	Alogliptin	0	0	0	0	0	0	1	0	1	1	0	0
8	Ambrisentan	0	0	1	0	0	1	0	0	1	1	0	1
9	Anagliptin	0	0	1	0	0	0	0	0	1	1	0	0
10	Anagrelide	0	1	1	0	0	1	0	0	1	1	1	1
11	Aprepitant	0	0	1	0	0	0	0	1	1	0	0	0
12	Asunaprevir	0	0	0	0	0	0	0	0	1	0	1	0
13	Atovaquone	1	0	0	0	0	0	0	0	1	0	0	1
14	Axitinib	1	1	1	0	0	0	1	0	0	0	1	0
15	Azilsartan	0	0	1	0	0	0	0	0	1	0	0	0
16	Bazedoxifene	0	0	0	0	0	0	1	0	1	0	0	0
17	Bixalomer	0	0	1	0	0	0	0	0	1	1	1	0
18	Blonanserin	0	0	1	0	0	0	0	1	0	0	0	0
19	Bosentan	1	0	1	1	0	1	0	1	1	1	1	1
20	Bosutinib	1	1	1	0	0	1	0	0	0	0	1	0
21	Canagliflozin	0	0	0	0	0	0	0	0	1	0	0	0
22	Clozapine	1	0	1	1	0	0	0	1	0	1	0	1
23	Crizotinib	1	1	0	0	1	1	1	0	0	0	1	1
24	Dabigatran	0	0	1	0	0	0	1	0	1	0	1	0
25	Daclatasvir	0	0	0	0	0	0	0	0	1	0	0	0
26	Dapagliflozin	0	0	1	0	0	0	0	0	1	0	0	0
27	Darunavir	0	0	0	0	0	1	0	1	1	0	0	1
28	Delamanid	0	0	0	0	0	1	1	0	1	0	1	1
29	Dienogest	0	0	0	0	0	0	0	1	1	0	0	0
30	Dolutegravir	0	0	1	0	0	1	0	0	1	0	0	1
31	Dutasteride	0	0	0	0	0	0	0	1	1	0	0	0

No.	Drug	F0	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11
32	Eldecalcitol	0	0	1	0	0	0	0	0	1	0	1	0
33	Eltrombopag	0	0	1	0	0	1	0	0	1	0	0	1
34	Empagliflozin	0	0	1	0	0	0	0	0	1	0	1	0
35	Emtricitabine	0	0	0	0	0	1	0	1	1	0	0	1
36	Entecavir	0	0	1	0	0	0	1	1	1	0	0	0
37	Enzalutamide	0	0	0	0	0	0	0	0	0	0	0	0
38	Eplerenon	1	0	1	0	0	0	1	1	1	0	1	0
39	Escitalopram	0	0	1	0	0	0	0	0	1	0	1	0
40	Eszopiclone	0	0	1	0	0	0	1	0	1	0	1	0
41	Etravirine	0	0	0	0	0	1	0	1	1	0	0	1
42	Ezetimibe	0	0	0	0	1	0	0	1	1	0	0	0
43	Ferric citrate	1	0	1	0	0	0	0	0	1	0	1	0
44	Fesoterodine	0	0	1	0	0	0	1	0	1	0	1	0
45	Fingolimod	0	0	0	0	0	1	0	0	1	0	1	1
46	Gabapentin	1	0	1	1	0	0	0	1	1	0	0	0
47	Gabapentin Enacarbil	1	0	0	0	0	0	1	0	1	0	1	0
48	Galantamine	0	0	1	1	0	0	0	0	1	0	1	0
49	Garenoxacin	0	0	0	0	0	0	0	1	0	0	0	0
50	Iguratimod	0	0	1	0	0	0	0	0	1	0	1	1
51	Imidafenacin	1	0	1	0	0	0	0	1	1	0	1	0
52	Ipraglifrozin	0	0	1	0	0	0	0	0	1	0	0	0
53	Irbesartan	0	0	1	0	0	0	0	1	0	0	0	0
54	Istradefylline	0	0	1	0	0	0	0	0	1	0	0	0
55	Lanthanum	0	0	1	0	0	0	0	1	1	0	1	0
56	Letrozole	0	0	0	0	0	0	0	1	1	0	0	1
57	Levetiracetam	0	0	1	0	0	0	0	0	1	0	0	0
58	Linagliptin	0	0	0	0	0	0	1	0	1	0	0	0
59	Lubiprostone	0	0	0	0	1	0	0	0	1	0	1	0
60	Luseogliflozin	0	0	1	0	0	0	0	0	1	0	0	0
61	Maraviroc	1	0	1	0	0	1	0	1	1	1	0	1
62	Memantine	1	0	1	1	0	0	0	0	1	0	1	0
63	Methadone	0	0	1	0	1	0	0	0	0	0	0	1
64	Miglitol	0	0	1	0	0	0	0	1	1	0	1	0
65	Miglustat	1	0	0	0	1	1	0	0	0	0	0	1
66	Minodronic Acid	0	0	0	0	0	0	0	1	1	0	0	0

No.	Drug	F0	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11
67	Mirabegron	0	0	0	0	0	0	0	0	1	0	0	0
68	Mirtazapine	0	0	1	0	0	0	0	1	1	0	0	0
69	Modafinil	0	0	0	0	0	1	0	1	1	0	0	0
70	Moxifloxacin	0	0	0	0	0	0	1	1	1	0	0	0
71	Mozavaptan	0	0	0	0	0	1	0	1	0	0	1	1
72	Nalfurafine	0	0	1	0	0	0	0	1	1	0	1	0
73	Nilotinib	1	1	1	0	1	1	0	1	0	0	1	1
74	Omega-3 fatty acid	0	0	1	0	0	0	0	0	1	0	1	0
75	Paliperidone	0	0	1	0	0	0	0	0	1	0	0	0
76	Pancrelipase	1	0	0	0	1	0	0	0	1	1	0	0
77	Pazopanib	1	1	0	0	1	1	1	0	0	1	0	1
78	Pirfenidone	1	0	1	1	1	1	0	1	0	1	1	0
79	Prasugrel	0	0	1	0	0	0	0	0	1	0	1	0
80	Raltegravir	0	0	0	0	0	1	0	1	1	0	0	1
81	Ramelteon	0	0	0	0	0	0	0	0	1	0	0	0
82	Regorafenib	1	1	1	0	1	0	1	0	0	1	1	0
83	Repaglinide	0	0	1	0	0	0	0	0	1	0	0	0
84	Rilpivirine	0	0	0	0	0	1	0	0	1	0	1	1
85	Riociguat	0	0	1	0	0	1	1	0	1	1	1	1
86	Ropinirole	1	0	1	1	0	0	0	1	0	0	0	0
87	Rosuvastatin	0	0	1	0	0	0	1	1	1	0	1	0
88	Rufinamide	1	0	1	1	0	0	0	0	1	1	1	0
89	Saxagliptin	0	0	1	0	0	0	0	0	1	0	0	0
90	Sertraline	0	0	1	0	0	0	0	1	0	0	0	0
91	Silodosin	0	0	0	0	1	0	0	1	1	0	0	0
92	Simeprevir	0	0	0	0	0	0	0	0	1	0	1	0
93	Sitafloxacin	0	0	1	0	0	0	0	1	0	0	1	0
94	Sitagliptin	0	0	1	0	0	0	0	1	1	0	0	0
95	Solifenacin	0	0	1	0	0	0	0	1	1	0	1	0
96	Sorafenib	1	1	0	0	1	0	0	1	0	0	1	1
97	Suvorexant	0	0	1	0	0	0	1	0	1	0	1	0
98	Tafamidis	0	0	0	0	0	1	0	0	0	0	0	1
99	Tapentadol	0	0	1	0	1	0	0	0	0	0	0	0
100	Telaprevir	1	0	0	0	0	0	0	0	1	0	0	1
101	Teneligliptin	0	0	1	0	0	0	0	0	1	0	0	0

No.	Drug	F0	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11
102	Tetrabenazine	0	0	1	0	0	1	0	0	0	0	1	1
103	Tofacitinib	0	0	0	0	0	0	1	0	1	0	1	1
104	Tofogliflozin	0	0	0	0	0	0	1	0	1	1	1	0
105	Tolterodine	0	0	0	0	1	0	1	1	1	0	1	0
106	Topiroxostat	1	0	1	1	0	0	0	0	1	0	1	0
107	Vaniprevir	0	0	0	0	0	0	0	0	1	0	1	0
108	Varenicline Tartrate	1	0	1	1	0	0	1	1	1	0	1	0
109	Vemurafenib	0	1	0	0	0	1	0	0	0	0	1	1
110	Vildagliptin	0	0	1	0	0	0	0	0	1	0	1	0
111	Voriconazole	0	0	1	0	0	0	0	1	0	0	1	1
112	Vorinostat	1	1	1	0	1	1	0	0	0	0	1	1
113	Zinc acetate	0	0	1	0	0	1	0	1	0	0	0	1

F0: “Lower-dose prescription drugs”

F1: Antineoplastic agents

F2: Dose range (The approved dosage is within a certain width.)

F3: Maintenance dose different from the initial dose

F4: Upward/downward dose adjustment (Products with description such as “dose may be adjusted” or “dose may be reduced” according to the patient’s condition in the approved dosage)

F5: Orphan drugs

F6: Bridging strategy or multi-regional clinical trial

F7: Approved before 2010

F8: Dose finding study (A study to examine the efficacy and safety comparing two or more fixed dose was conducted for the product.)

F9: Lower dose in pivotal study (Lower dose was examined in phase III study or latest phase study before approval.)

F10: Safety concern (Products for which adverse effects were considered in dose selection.)

F11 Approval condition (Requirement for conducting post-marketing clinical study or all-case survey.)

For each factor, “1” indicates yes, “0” indicates no. “Lower-dose prescription drugs” were products whose percentage of prescriptions corresponding to the category of doses lower than the approved dose, or the approved maintenance dose if the initial dose is set, was ≥ 30% in the database of either MDV or JammNet.

2.3.2 Lower-dose prescription drugs

Twenty-seven of the 113 (23.9%) investigated products were identified as “lower-dose prescription drugs.” The number and percentage of prescriptions by daily dose category in each database for the 27 products are shown in Table 3. Although there were a few differences, prescription trends were roughly similar between the two databases.

Table 3. List of the “lower-dose prescription drugs.”

Drug	Categories of daily dose (mg)		Prescriptions in the database				Lower-dose prescriptions	
			MDV		JammNet		MDV	JammNet
			Number	Percent	Number	Percent	Percent	Percent
Afatinib	DSP	≥ 20, < 40	6,572	52.5%	171	61.1%	52.5%	61.1%
	AD	≥ 40, ≤ 50	5,716	45.6%	109	38.9%		
		> 50	241	1.9%	0	0.0%		
Atovaquone	AD	< 1500	1,127	13.4%	68	34.3%	13.4%	34.3%
		1500	7,148	85.0%	129	65.2%		
		> 1500	133	1.6%	1	0.5%		
Axitinib	DSP AD	< 4	252	3.9%	0	0.0%	44.7%	23.4%
		≥ 4, < 10	2,664	40.8%	32	23.4%		
		≥ 10, ≤ 20	3,575	54.8%	105	76.6%		
		> 20	33	0.5%	0	0.0%		
Bosentan	AID AMD	< 125	1,086	13.4%	28	13.4%	56.7%	52.6%
		≥ 125, < 250	3,497	43.3%	82	39.2%		
		250	3,424	42.4%	99	47.4%		
		> 250	72	0.9%	0	0.0%		
Bosutinib	DSP AD	< 400	356	35.5%	63	77.8%	55.7%	100.0%
		≥ 400, < 500	203	20.2%	18	22.2%		
		≥ 500, ≤ 600	419	41.8%	0	0.0%		
		> 600	25	2.5%	0	0.0%		
Clozapine	AID AMD	≥ 12.5, < 200	981	20.6%	115	36.9%	20.6%	36.9%
		≥ 200, ≤ 600	3,768	79.1%	197	63.1%		
		> 600	14	0.3%	0	0.0%		
Crizotinib	DSP AD	< 250mg	349	18.7%	0	0.0%	31.0%	10.7%
		≥ 250, < 500	228	12.2%	3	10.7%		
		500	1,257	67.5%	25	89.3%		
		> 500	29	1.6%	0	0.0%		
Eplerenone	AD	< 50	45,147	38.2%	1,658	33.4%	38.2%	33.4%
		≥ 50, ≤ 100	72,712	61.6%	3,301	66.5%		
		> 100	204	0.2%	4	0.1%		

Drug	Categories of daily dose (mg)		Prescriptions in the database				Lower-dose prescriptions	
			MDV		JammNet		MDV	JammNet
			Number	Percent	Number	Percent	Percent	Percent
Ferric citrate	AD	< 1500	17,078	52.4%	746	40.3%	52.4%	40.3%
		≥ 1500, ≤ 6000	15,482	47.5%	1,104	59.7%		
		> 6000	2	0.0%	0	0.0%		
Gabapentin Enacarbil	DSP	< 300	1	0.0%	0	0.0%	48.5%	46.4%
		≥ 300, < 600	1,051	48.5%	173	46.4%		
	AD	600	1,095	50.5%	200	53.6%		
		> 600	22	1.0%	0	0.0%		
Imidafenacin	AD	< 0.2	22,924	34.7%	888	31.0%	34.7%	31.0%
		≥ 0.2, ≤ 0.4	43,043	65.2%	1,973	69.0%		
		< 0.4	45	0.1%	0	0.0%		
Maraviroc	DSP	≥ 150, < 600	28	62.2%	0	0.0%	62.2%	0.0%
	AD	600	17	37.8%	5	100.0%		
Memantine	AID	< 5	217	0.2%	0	0.0%	50.3%	40.0%
		≥ 5, <10	25,954	18.4%	187	12.4%		
	DSP	≥ 10, < 20	44,974	31.8%	414	27.5%		
	AMD	20	68,336	48.3%	887	59.0%		
		> 20	1,951	1.4%	15	1.0%		
Miglustat	DSP	≥ 200, < 600	3	37.5%	0	NA	37.5%	NA
	AD	600	1	12.5%	0	NA		
		> 600	4	50.0%	0	NA		
Nilotinib	DSP	< 400mg	1,375	24.0%	2	1.5%	38.8%	18.2%
		≥ 400, < 600	849	14.8%	22	16.7%		
	AD	≥ 600, ≤ 800	3,473	60.5%	108	81.8%		
		> 800mg	42	0.7%	0	0.0%		
Pancrelipase	AD	< 1800	29,220	45.3%	636	42.0%	45.3%	42.0%
		1800	33,802	52.4%	854	56.4%		
		> 1800	1,518	2.4%	24	1.6%		
Pazopanib	DSP	> 200, < 800	2,521	57.5%	48	64.0%	57.5%	64.0%
	AD	800	1,795	41.0%	27	36.0%		
		> 800	66	1.5%	0	0.0%		

Drug		Categories of daily dose (mg)	Prescriptions in the database				Lower-dose prescriptions	
			MDV		JammNet		MDV	JammNet
			Number	Percent	Number	Percent	Percent	Percent
Pirfenidone		< 600	322	3.4%	1	1.1%	82.8%	72.6%
	AID	≥ 600, < 1200	3,420	36.6%	32	33.7%		
	DSP	≥ 1200, < 1800	3,991	42.7%	36	37.9%		
	AMD	1800	1,545	16.5%	26	27.4%		
		> 1800	58	0.6%	0	0.0%		
Regorafenib		< 80	142	3.6%	6	7.1%	68.7%	56.5%
	DSP	≥ 80, < 160	2,577	65.1%	42	49.4%		
	AD	160	1,210	30.6%	37	43.5%		
		> 160	28	0.7%	0	0.0%		
Ropinirole		< 0.75	386	6.2%	4	4.5%	32.9%	21.6%
	AID	≥ 0.75, < 3	1,676	26.7%	15	17.0%		
	AMD	≥ 3, ≤ 15	4,203	67.0%	69	78.4%		
		> 15	8	0.1%	0	0.0%		
Rufinamide		< 400	22	4.9%	0	0.0%	71.2%	31.0%
	AID	≥ 400, < 1800	300	66.4%	9	31.0%		
	AMD	≥ 1800, ≤ 3200	127	28.1%	20	69.0%		
		> 3200	3	0.7%	0	0.0%		
Sorafenib	DSP	≥ 200, < 800	10,170	77.2%	54	72.0%	77.2%	72.0%
	AD	800	2,926	22.2%	21	28.0%		
		> 800	81	0.6%	0	0.0%		
Telaprevir		< 2250	207	98.1%	0	NA	98.1%	NA
	AD	2250	3	1.4%	0	NA		
		> 2250	2	0.9%	0	NA		
Topiroxostat		< 40	1,542	14.6%	285	16.9%	92.3%	95.4%
	AID	≥ 40, < 120	8,204	77.7%	1,322	78.5%		
	AMD	≥ 120, ≤ 160	799	7.6%	77	4.6%		
		> 160	18	0.2%	0	0.0%		
Varenicline		< 0.5	1	0.0%	0	0.0%	7.8%	40.4%
	AID	≥ 0.5, < 1	78	0.9%	815	19.4%		
	DSP	≥ 1, < 2	614	7.0%	883	21.0%		
	AMD	2	5,436	61.5%	2,506	59.6%		
		> 2	2,705	30.6%	2	0.0%		

Drug		Categories of daily dose (mg)	Prescriptions in the database				Lower-dose prescriptions	
			MDV		JammNet		MDV	JammNet
			Number	Percent	Number	Percent	Percent	Percent
Vorinostat		< 300	23	29.5%	0	NA	92.3%	NA
	DSP	≥ 300, < 400	49	62.8%	0	NA		
	AD	400	6	7.7%	0	NA		

AD: approved dose AID: approved initial dose AMD: approved maintenance dose
DSP: dose for special population IDSP: initial dose for special population
MDSP: maintenance dose for special population

The proportions of "lower-dose prescription drugs" classified based on the ATC code first level, anatomical main group, are shown in Fig 2. A relatively large number of products classified as "L; antineoplastic and immunomodulating agents" and "N; nervous system" was identified as "lower-dose prescription drugs," 52.6% (10/19) and 29.2% (7/24) respectively.

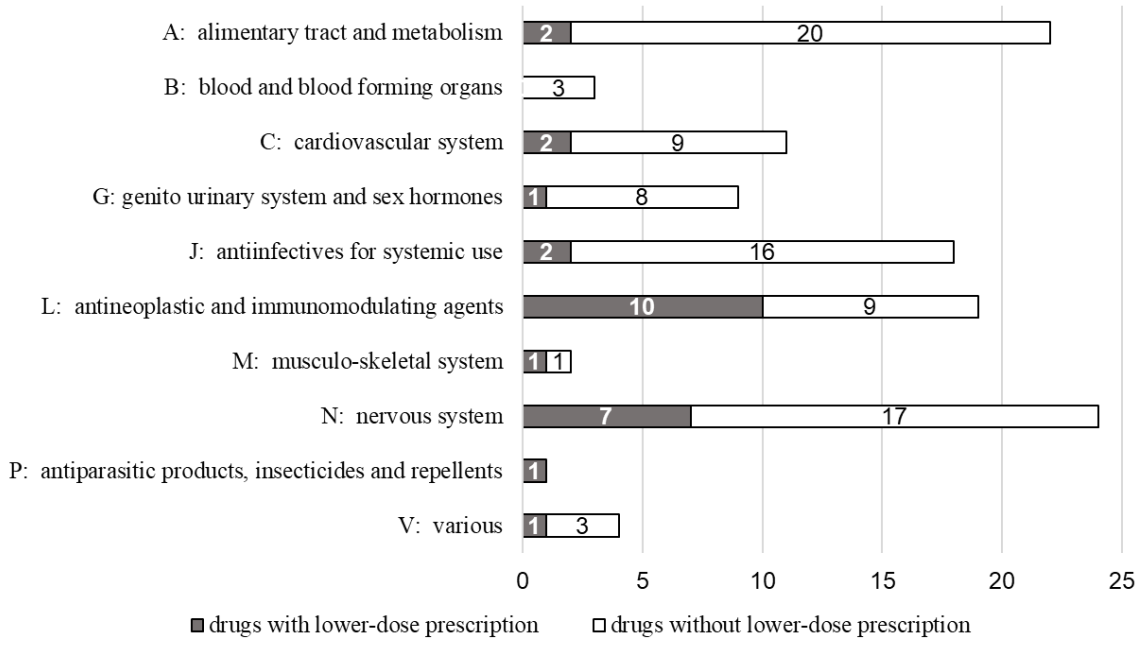


Fig 2. Number of drugs with or without lower-dose prescriptions according to the ATC classification.

Regarding the distribution of daily dose in the database of MDV, the median daily dose was less than the approved dose (or the approved maintenance dose if the initial dose is set) for 15 products. For these 15 products, the median and quartile points of the prescribed daily dose standardized by the minimum approved dose (the minimum approved dose equal to 1) are shown in Fig 3 and Table 4. The data clearly indicated that the prescription doses in the actual situation were considerably lower than the approved dose.

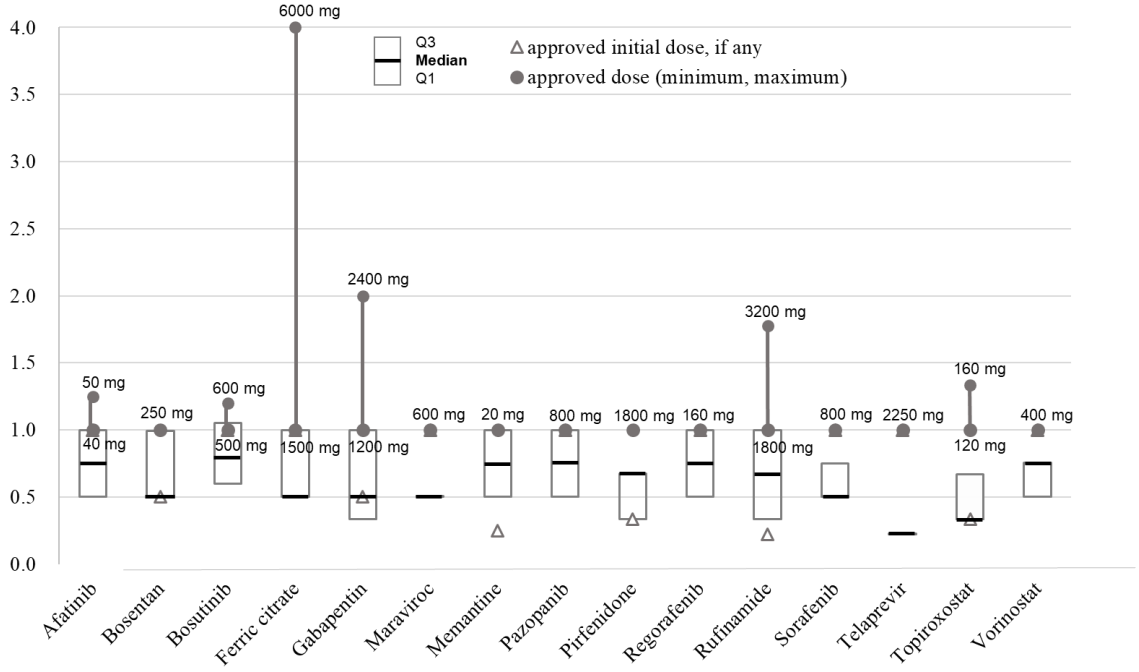


Fig 3. Median and quartile points of frequency distribution of prescribed dosage standardized by the minimum approved dose.

The box plots show the median and quartile points of the prescribed daily dose. The red lines indicate the median. The blue triangles indicate the approved initial dose (different from the maintenance dose), the orange circles indicate the approved maintenance dose and the orange full lines indicate the range (if the initial dose is not set, the approved dose is the same as the approved maintenance dose), and the numbers in black indicate the real minimum and maximum of the approved maintenance doses.

Table 4. Median and quartile points of the prescribed daily dose.

Drug	Detailed statement of the approved dosage (mg)			Frequency distribution of the prescribed daily dose (mg)		
	Initial dose	Maintenance dose (minimum)	(maximum)	First quartile	Median	Third quartile
Afatinib	40	40	50	20	30	40
Bosentan	125	250	250	124	124	248
Bosutinib	500	500	600	300	400	500
Ferric citrate	1500	1500	6000	750	750	1500
Gabapentin	600	1200	2400	400	600	1200
Maraviroc	600	600	600	300	300	600
Memantine	5	20	20	10	15	20
Pazopanib	800	800	800	400	600	800
Pirfenidone	600	1800	1800	600	1200	1200
Regorafenib	160	160	160	80	120	160
Rufinamide	400	1800	3200	600	1200	1800
Sorafenib	800	800	800	400	400	600
Telaprevir	2250	2250	2250	500	500	500
Topiroxostat	40	120	160	40	40	80
Vorinostat	400	400	400	200	300	300

2.3.3 Univariate and multivariate regression analyses

The results of the univariate analysis are shown in Table 5.

Table 5. Results of the univariate analysis.

Parameter		Proportion of lower-dose prescription drugs		Odds ratio	(95% CI)	p value
ATC classification						
Antineoplastic agents	Yes	9/12	75.0%	13.83	(3.40–56.24)	< 0.001
	No	18/101	17.8%			
Detailed statement of the approved dosage						
Dose range [a]	Yes	19/67	28.4%	1.88	(0.74–4.76)	0.183
	No	8/46	17.4%			
Maintenance dose different from the initial dose	Yes	9/10	90.0%	42.50	(5.06–356.79)	< 0.001
	No	18/103	17.5%			
Upward/downward dose adjustment [b]	Yes	9/15	60.0%	6.67	(2.10–21.11)	0.001
	No	18/98	18.4%			
Clinical data package						
Orphan drugs	Yes	9/28	32.1%	1.76	(0.68–4.55)	0.241
	No	18/85	21.2%			
Bridging strategy or multi-regional clinical trial	Yes	8/23	34.8%	1.99	(0.74–5.40)	0.175
	No	19/90	21.1%			
First approved before 2010	Yes	11/42	26.2 %	0.82	(0.34, 1.99)	0.660
	No	16/71	22.5 %			
Dose finding study [c]	Yes	14/85	16.5%	0.23	(0.09–0.58)	0.002
	No	13/28	46.4%			
Lower dose in pivotal study [d]	Yes	8/16	50.0%	4.11	(1.37–12.34)	0.012
	No	19/97	19.6%			
Safety concern [e]	Yes	18/53	34.0%	2.91	(1.17–7.23)	0.021
	No	9/60	15.0%			
Post-marketing requirement						
Approval conditions [f]	Yes	11/34	32.4%	1.88	(0.76–4.65)	0.170
	No	16/79	20.3%			

CI: confidence interval.

[a] The approved dosage is within a certain width.

[b] Products with description such as “dose may be adjusted” or “dose may be reduced” according to the patient’s condition in the approved dosage

[c] A study to examine the efficacy and safety comparing two or more fixed dose was conducted for the product.

[d] Lower dose was examined in phase III study or latest phase study before approval.

[e] Products for which adverse effects were considered in dose selection.

[f] Requirement for conducting post-marketing clinical study or all-case survey.

Six factors, namely, “antineoplastic agents,” “maintenance dose different from initial dose,” “upward/downward dose adjustment,” “dose finding study,” “lower dose in pivotal study,” and “safety concern,” were selected as candidates for the multivariate analysis. A strong association between “antineoplastic agents” and “dose finding study” (Cramér's V = 0.534) was identified (Table 6), and we selected five factors excluding “dose finding study” as exploratory variables for the multivariate analysis. The results of the multivariate analysis revealed that “antineoplastic agents,” “maintenance dose different from the initial dose,” and “upward/downward dose adjustment” significantly associated with “lower-dose prescription drugs” ($p < 0.05$) (Table 7).

Table 6. Results of Cramer's coefficient of association.

	Parameter	1	2	3	4	5	6
1	Antineoplastic agents	-	0.107	0.373	0.534	0.107	0.252
2	Maintenance dose different from the initial dose	-	-	0.030	0.038	0.231	0.144
3	Upward/downward dose adjustment	-	-	-	0.380	0.117	0.144
4	Dose finding study	-	-	-	-	0.002	0.036
5	lower dose in pivotal study	-	-	-	-	-	0.025
6	Safety concern	-	-	-	-	-	-

Table 7. Results of the multivariate analysis.

Parameter	Odds ratio	(95% CI)	p value
Antineoplastic agents	14.44	(2.73–76.51)	0.002
Maintenance dose different from the initial dose	79.82	(8.49–750.26)	< 0.001
Upward/downward dose adjustment [a]	6.05	(1.33–27.59)	0.020
Lower dose in pivotal study [b]	2.20	(0.42–11.39)	0.349
Safety concern [c]	1.54	(0.42–5.61)	0.514

CI: confidence interval.

[a] Products with description such as “dose may be adjusted” or “dose may be reduced” according to a patient’s condition in the approved dosage.

[b] Lower dose was examined in phase III study or latest phase study before approval.

[c] Products for which adverse effects were considered in the dose selection.

2.4 Discussion

In Research 1, with respect to the actual situation of lower dose prescription in clinical use, we identified 27 products (23.9%) as “lower-dose prescription drugs.” For the factors that might lead to lower dose prescriptions in post-marketing use, the results showed that factors such as ATC classification and detailed statement of the approved dosage significantly influenced “lower-dose prescription drugs,” but those related to clinical data package and post-marketing requirement did not.

“Antineoplastic agents” in ATC classification was strongly associated with no “dose finding study” in clinical data package; we thought that priority was given to satisfying clinical needs in the development process and that dose selection was not made based on sufficient study results. This is in accord with the fact that the U.S. Food and Drug Administration and some relevant scientific societies have been discussing a better approach to dose selection in the clinical development and dose optimization in post-marketing for oncology drugs [9, 12].

It was suggested that drugs with “maintenance dose different from the initial dose” and “upward/downward dose adjustment” in the statement of the approved dosage might lead to lower dose prescription. For many products with different initial dose and maintenance dose, gradual dose titration from the initial low dose is recommended in the product label to ensure initial tolerability. It is reasonable to assume that the dose of such products cannot be increased to an effective level due to adverse effects or may not be increased further based on clinical judgment of sufficient efficacy. That is, products with “maintenance dose different from the initial dose” and “upward/downward dose adjustment” might have a large variation in response among patients, which makes it difficult to adjust dosage for individual patients.

We also investigated relevant factors related to “lower dose prescription drugs” from the perspective of clinical data package and post-marketing requirement. Although the proportion of “lower-dose prescription drugs” was marginally high in drugs with “safety concern” and “approval conditions,” these factors were not identified to be related to “lower-dose prescription drugs.” This shows a limitation in predicting lower dose prescriptions in various actual post-marketing situations from the results of clinical trials before approval, and also a possibility that the approved dose may not be identical to the

optimal dose after marketing.

3 Research 2 (Relationship between dose discontinuation and reduction due to safety issues in pivotal studies and lower-dose prescriptions in the post-marketing situation.)

3.1 Objectives

We assumed that for "lower-dose prescription drugs," their efficacy and recommended dose had been evaluated based on results of pivotal studies in which medication was discontinued or its dosage was reduced due to safety issues for considerable number of patients, or which lacked enough efficacy and safety data in the elderly. Therefore, in Research 2, for the purpose of seeking out signals suggesting lower-dose prescription in the post-marketing situation, we extracted the number of patients whose medication was discontinued or its dosage was reduced due to adverse events (AEs) among those who were exposed to the approved dose range in pivotal studies, and also the number of elderly patients participated in those trials. Then we analyzed the relationship between the proportions of such patients and "lower-dose prescription drugs" identified in Research 1. We excluded antineoplastic agents from the analysis because these drugs have characteristics considerably different from those of other pharmaceutical products in terms of dosage selection in the clinical development process.

3.2 Materials and methods

3.2.1 Drugs examined

We created a data set of 101 products after excluding 12 antineoplastic agents from the Research 1 dataset of 113 products, using the ATC code, products of "L01 antineoplastic agents."

3.2.2 Data sources and extracted data

For the selected 101 products, we identified pivotal studies for each product which were regarded as (a) main study(ies) for the assessment of efficacy and safety in the review based on the new drug application dossier (CTD) and the review report, which are opened to the public after the approval. Then we extracted the data below for those pivotal studies from the Module 2 of CTD. When there was more than one pivotal study for a product, we combined the data.

1) Number of patients who were exposed to the approved dose range. Patients to whom at least one dose of the drug was administrated were counted. When some dosage arms were out of the approved dose range in the pivotal study, we omitted the arms to count the number of exposed patients.
2) Number of patients who withdrew from the pivotal study. Patients who withdrew from the study after receiving at least one dose of the drug for any reasons were counted.
3) Number of patients whose medication was discontinued due to AEs in the pivotal study. Patients whose medication was discontinued due to AEs after receiving at least one dose of the drug in the pivotal studies were counted. In this context, medication means administration of the drug.
4) Number of patients whose medication was suspended, or its dosage was reduced in the pivotal study. Patients whose medication was temporarily suspended or its dosage was reduced after receiving at least one dose of the drug due to AEs in the pivotal studies were counted. In this context, medication means administration of the drug. When there were no descriptions of the rules on dose reduction or suspension in the study protocol and no descriptions in the study result, we judged

that there were no patients whose medication was suspended or its dosage was reduced. In some cases, the numbers of patients whose medication was suspended, or its dosage was reduced were shown separately. In that case, we combined these numbers although they may be duplicated.

5) Number of elderly patients who were exposed to the approved dose range in the pivotal study. Patients aged 65 or over who were administrated at least one dose of the drug in the pivotal studies were counted.

3.2.3 Analysis

We calculated the proportions (percentages) of patients falling into the definition 2) to 5) to patients 1) in 3.2.2 and analyzed the relationship between these proportions and “lower-dose prescription drugs” defined in Research 1 using Mann-Whitney’s U-test.

3.3 Result

3.3.1 Data set

We showed the proportions (percentages) of patients who withdrew from the study or whose medication was discontinued, reduced or suspended due to AEs, and the proportions of elderly patients in the pivotal studies for each of the 101 products in Table 8.

Table 8. Percentages of patients who withdrew from the study or whose medication was discontinued, reduced or suspended and percentages of elderly patients in pivotal studies.

Drug	F0	Withdrawal from study	Discontinuation due to AEs	Reduction or Suspension due to AEs	Elderly patients
Abiraterone	0	74.2%	16.3%	17.6%	72.7%
Acamprosate	0	32.5%	32.5%	0.0%	17.2%
Acotiamide	0	2.7%	0.7%	0.0%	0.0%
Aliskiren	0	5.1%	1.4%	0.0%	12.8%
Alogliptin	0	10.7%	1.5%	0.0%	18.3%
Ambrisentan	0	8.4%	4.5%	3.5%	20.3%
Anagliptin	0	1.7%	0.0%	0.0%	31.4%
Aprepitant	0	12.7%	4.9%	0.0%	19.2%
Asunaprevir	0	12.6%	5.0%	0.0%	40.1%
Atovaquone	1	64.4%	11.9%	0.0%	0.0%
Azilsartan	0	8.2%	1.6%	0.0%	24.1%
Bazedoxifene	0	33.1%	15.1%	0.0%	25.9%
Bixalomer	0	16.4%	5.5%	0.0%	36.4%
Blonanserin	0	27.0%	18.2%	0.0%	8.1%
Bosentan	1	NA	3.2%	NA	NA
Canagliflozin	0	6.7%	1.7%	0.0%	30.9%
Clozapine	1	18.6%	18.6%	65.1%	0.0%
Dabigatran	0	22.7%	5.3%	24.5%	83.6%
Daclatasvir	0	12.6%	5.0%	0.0%	40.1%
Dapagliflozin	0	8.0%	5.7%	0.0%	27.6%
Darunavir	0	12.3%	4.9%	0.0%	NA
Delamanid	0	11.2%	2.5%	0.0%	0.0%
Dienogest	0	6.2%	4.7%	4.7%	0.0%
Dolutegravir	0	NA	2.4%	0.0%	NA
Dutasteride	0	15.5%	8.3%	0.0%	64.8%
Eldecalcitol	0	19.1%	5.9%	2.8%	87.5%
Eltrombopag	0	6.7%	6.7%	0.0%	40.0%
Empagliflozin	0	9.4%	1.5%	0.0%	25.1%
Emtricitabine	0	22.8%	7.7%	0.0%	NA

Drug	F0	Withdrawal from study	Discontinuation due to AEs	Reduction or Suspension due to AEs	Elderly patients
Entecavir	0	4.4%	1.1%	0.0%	4.1%
Enzalutamide	0	71.1%	16.0%	93.0%	71.0%
Eplerenon	1	33.2%	6.7%	0.0%	26.1%
Escitalopram	0	13.0%	4.6%	0.0%	0.0%
Eszopiclone	0	5.7%	1.4%	0.0%	0.0%
Etravirine	0	8.3%	5.8%	0.0%	1.0%
Ezetimibe	0	17.6%	1.7%	0.0%	23.5%
Ferric citrate	1	15.9%	6.3%	0.6%	43.2%
Fesoterodine	0	14.0%	3.8%	0.0%	32.0%
Fingolimod	0	6.7%	6.6%	5.3%	0.0%
Gabapentin	1	7.1%	5.5%	0.8%	3.1%
Gabapentin Enacarbil	1	12.3%	7.9%	0.9%	NA
Galantamine	0	21.1%	21.1%	2.6%	87.2%
Garenoxacin	0	NA	2.2%	0.0%	31.9%
Iguratimod	0	36.9%	12.1%	0.0%	23.5%
Imidafenacin	1	12.8%	3.4%	0.0%	36.1%
Ipraglifrozin	0	6.5%	3.2%	0.0%	38.7%
Irbesartan	0	6.5%	3.6%	0.0%	6.5%
Istradefylline	0	8.5%	2.4%	0.0%	59.9%
Lanthanum	0	NA	3.2%	0.0%	28.6%
Letrozole	0	9.7%	3.2%	0.0%	25.0%
Levetiracetam	0	15.0%	7.6%	0.0%	0.0%
Linagliptin	0	1.9%	1.9%	0.0%	41.5%
Lubiprostone	0	4.8%	3.2%	1.6%	6.8%
Luseogliflozin	0	3.8%	0.0%	1.3%	72.2%
Maraviroc	1	32.4%	3.8%	10.3%	1.2%
Memantine	1	13.4%	7.6%	0.0%	84.1%
Methadone	0	15.0%	15.0%	0.0%	30.0%
Miglitol	0	8.0%	8.0%	0.0%	21.3%
Miglustat	1	0.0%	0.0%	0.0%	0.0%
Minodronic Acid	0	23.7%	15.3%	0.0%	84.4%
Mirabegron	0	8.9%	3.4%	0.0%	39.0%
Mirtazapine	0	25.0%	10.4%	0.0%	6.3%

Drug	F0	Withdrawal from study	Discontinuation due to AEs	Reduction or Suspension due to AEs	Elderly patients
Modafinil	0	8.9%	6.7%	0.0%	0.0%
Moxifloxacin	0	13.4%	6.7%	0.0%	24.0%
Mozavaptan	0	7.1%	7.1%	0.0%	57.1%
Nalfurafine	0	2.7%	2.7%	1.8%	40.7%
Omega-3 fatty acid	0	3.1%	3.1%	0.0%	19.0%
Paliperidone	0	34.3%	9.0%	0.0%	12.7%
Pancrelipase	1	0.0%	0.0%	0.0%	45.5%
Pirfenidone	1	7.4%	18.5%	44.4%	62.0%
Prasugrel	0	23.5%	5.9%	0.0%	54.6%
Raltegravir	0	NA	2.2%	0.0%	1.9%
Ramelteon	0	4.2%	2.6%	0.0%	6.1%
Repaglinide	0	6.3%	4.7%	0.0%	39.1%
Rilpivirine	0	NA	3.4%	4.1%	0.3%
Riociguat	0	7.5%	2.9%	0.0%	42.8%
Ropinirole	1	NA	13.0%	0.0%	39.3%
Rosuvastatin	0	4.7%	3.3%	0.0%	28.0%
Rufinamide	1	13.8%	13.8%	24.1%	0.0%
Saxagliptin	0	12.7%	2.6%	0.0%	29.6%
Sertraline	0	51.1%	15.4%	0.0%	10.6%
Silodosin	0	12.0%	9.7%	0.0%	55.4%
Simeprevir	0	12.6%	1.8%	0.0%	28.1%
Sitafloxacin	0	0.0%	4.5%	0.0%	44.7%
Sitagliptin	0	4.9%	1.2%	0.0%	41.1%
Solifenacin	0	8.5%	5.9%	0.0%	42.6%
Suvorexant	0	14.0%	3.0%	0.0%	40.9%
Tafamidis	0	0.0%	0.0%	0.0%	40.0%
Tapentadol	0	32.7%	13.1%	NA	54.2%
Telaprevir	1	37.3%	35.7%	0.0%	0.0%
Teneligliptin	0	1.3%	1.3%	0.0%	29.9%
Tetrabenazine	0	NA	0.0%	0.0%	NA
Tofacitinib	0	22.1%	4.7%	6.9%	14.6%
Tofogliflozin	0	1.7%	1.7%	0.0%	31.0%
Tolterodine	0	11.4%	5.3%	0.0%	41.6%

Drug	F0	Withdrawal from study	Discontinuation due to AEs	Reduction or Suspension due to AEs	Elderly patients
Topiroxostat	1	9.3%	4.9%	0.0%	30.2%
Vaniprevir	0	5.9%	4.2%	0.0%	19.0%
Varenicline Tartrate	1	35.0%	9.5%	0.0%	2.0%
Vildagliptin	0	4.8%	2.1%	0.0%	36.2%
Voriconazole	0	36.1%	13.1%	0.0%	38.0%
Zinc acetate	0	0.0%	0.0%	10.8%	0.0%

F0: Lower-dose prescription drugs AE: Adverse Events NA: Not Available

3.3.2 Relationship with “lower-dose prescription drugs”

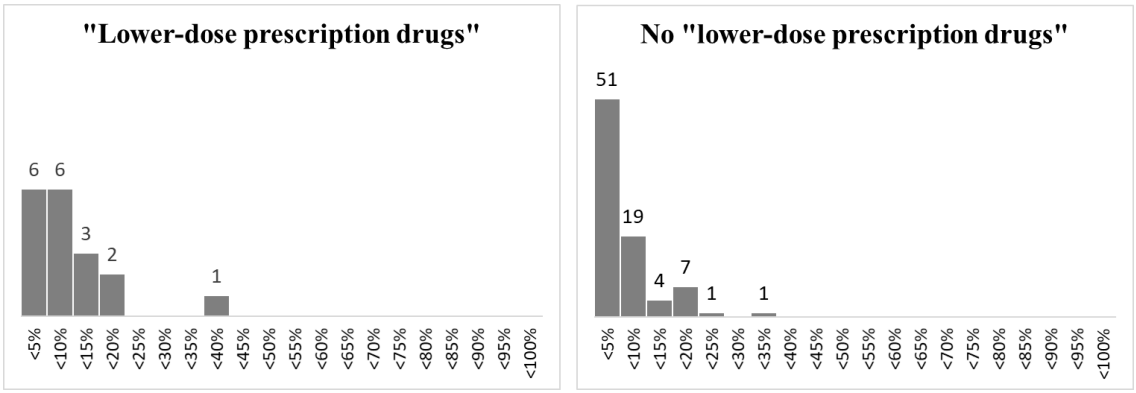
Relationship between the proportions of patients falling into the definition 2) to 5) to patients 1) in 3.2.2 and “lower-dose prescription drugs” defined in Research 1 is shown in Table 9. There was no statistical difference between the proportions of patients who withdrew from the pivotal study or elderly patients and “lower-dose prescription drugs.” The proportion of patients whose medication was discontinued due to AEs, and that of patients whose medication was reduced or suspended due to AEs were significantly higher in the “lower-dose prescription drug” ($p<0.029$, $p<0.045$, respectively). Histograms of the proportions of such patients are shown in Fig.4.

Table 9. Relationship between the proportions of patients who withdrew from the pivotal study or whose medication was discontinued, reduced or suspended due to AEs and elderly patients in the pivotal studies and "lower-dose prescription drugs."

	"Lower-dose prescription drugs"		**p value**
	Yes	**No**	
Number of drugs	**18**	**83**	
Withdrawal from the study			
Number of eligible drugs	16	77	0.118
Average (Standard deviation) (%)	19.6 (13.6)	14.2 (9.4)	
Median (Range) (%)	13.6 (0-64.4)	13.9 (0-74.2)	
Discontinuation due to AEs			
Number of eligible drugs	18	83	0.029
Average (Standard deviation) (%)	9.5 (8.3)	5.7 (5.5)	
Median (Range) (%)	7.2 (0-35.7)	4.5 (0-32.5)	
Reduction or Suspension due to AEs			
Number of eligible drugs	17	82	0.045
Average (Standard deviation) (%)	8.6 (18.2)	2.2 (10.7)	
Median (Range) (%)	0 (0-65.1)	0 (0-93.0)	
Elderly patients			
Number of eligible drugs	16	79	0.254
Average (Standard deviation) (%)	23.3 (25.8)	30.2 (22.7)	
Median (Range) (%)	14.6 (0-97.5)	28.6 (0-97.1)	

AEs: Adverse Events

(a) Discontinuation due to AEs



(b) Reduction or Suspension due to AEs

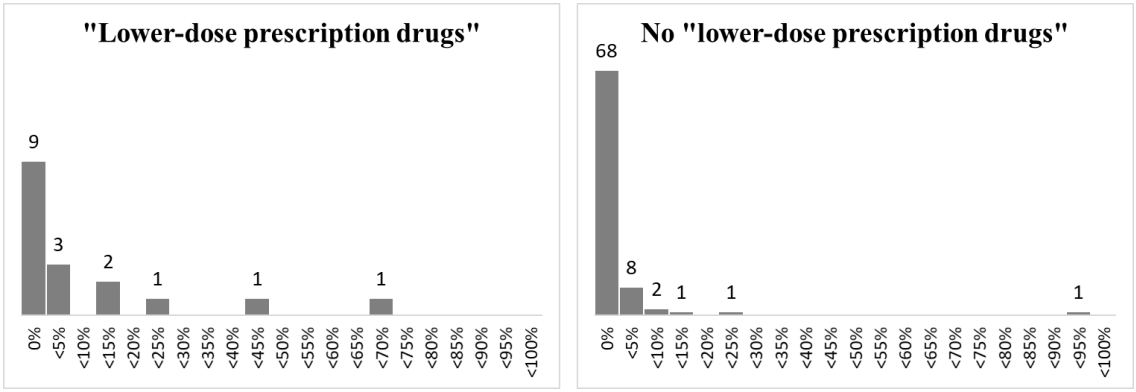


Fig 4. Histograms of the proportions of patients whose medication was discontinued (a), and reduced or suspended (b) due to AEs in the pivotal studies by “lower-dose prescription drugs” or not.

3.4 Discussion

The proportion of patients whose medication was discontinued, reduced or suspended due to AEs to those who were expose to the approved dose range in the pivotal studies were higher in “lower-dose prescription drugs” than in no “lower-dose prescription drugs.” This indicates that such drugs might lead to lower dose prescription in the post-marketing clinical use (Table 9).

Histograms in Fig.4 give the results that, for no “lower-dose prescription drugs,”

70 out of 83 products (84.3%) had less than 10% subjects whose medication was discontinued due to AEs, and 68 out of 82 products (82.9%) had no subjects whose medication was reduced or suspended due to AEs. On the contrary, for "lower-dose prescription drugs," such figures remained at a relatively low level; 12 out of 18 products (66.7%) had less than 10% subjects whose medication was discontinued due to AEs, and 9 out of 17 products (52.9%) had no subjects whose medication was reduced or suspended due to AEs. However, among the no "lower-dose prescription drugs," there were 2 products for which the medication was discontinued due to AEs for over 25% of the subjects and another 2 products for which the medication was reduced or suspended due to AEs for over 25% of the subjects (Fig 4). This also highlighted the difficulties in identifying drugs which might be used at lower dose in the post-marketing with a certain threshold. For Enzalutamide, a drug for prostate cancer categorized as ATC code "L02 Endocrine therapy," the medication was reduced or suspended due to AEs for 93% of subjects, though it was not a "lower-dose prescription drug." It might be owing to the fact that the protocol stipulated that the medication should be continued until onset of intolerable toxicity, initiation of new systemic antineoplastic therapy due to disease progression, death or withdrawal of consent.

On the other hand, although we hypothesized that for "lower-dose prescription drugs" their recommended dose had been evaluated based on results of pivotal studies that lacked enough data in elderly patients, the result of our analysis did not support the hypothesis. There was no significant difference on the proportion of elderly patients to the total patients who were exposed to the approved dose range in the pivotal studies between "lower-dose prescription drugs" and the rest of the drugs, suggesting that the state of participation of elderly patients in pivotal studies is not related to lower dose

prescription in the post-marketing clinical use.

4 Overall Discussion

We have clarified two points in the present studies. First, with respect to the actual situation of lower dose prescription in clinical use, we identified 27 products (23.9%) as "lower-dose prescription drugs." This means that the dose of approximately one-third or more prescriptions was lower than the approved dose among the 113 products approved in Japan between 2005 and 2014. We set the threshold value of "lower-dose prescription drugs" as ≥ 30% considering the proportion of elderly people (26.0%) in Japan as of January 2015 [13]. We believe this borderline can be one of the criteria for reconsidering the approved dosage, which is applicable to a greater number of patients. This finding is consistent with the results reported previously, that is, approximately 20% of 449 NMEs approved between 1980 and 1999 in the United States were subjected to dose change after approval, with approximately 80% of the changes involving switch to a lower dose [1], and approximately 60% of the products whose WHO DDD was changed between 1982 and 2000 were toward lower dose [2]. Research 1 highlighted the situation in which drugs are used at doses lower than the approved dose fairly frequently in the actual post-marketing scenario. Second, the results of Research 1 showed that the factors related to ATC classification and the detailed statement of the approved dosage significantly influenced "lower-dose prescription drugs." We also investigated relevant factors from the perspective of clinical data package and post-marketing requirement, but they were not identified to be related to "lower-dose prescription drugs," though the proportion of drugs with "safety concern" and "approval conditions" was marginally high for "lower-dose prescription drugs." This shows a limitation in predicting lower dose prescription in various actual post-marketing situations from the results of clinical trials before approval, and also a possibility that the approved dose may not be identical to the optimal dose after

marketing.

In addition, previous reports have suggested that the efficacy at low doses is not sufficiently studied during the development period because phase III trials mainly focus on the confirmation of efficacy; this is one of the reasons for the use of a lower dose of a drug post-marketing [1, 6]. In Research 1, although there was no statistically significant difference, several products of "lower dose in pivotal study" (lower dose was examined in phase III study or latest phase study before approval) corresponded to "lower-dose prescription drugs." This tendency suggests that when a dose lower than the approved dose is used in phase III trials, even if the dose was not ultimately selected as the approved dose, the lower dose might be used as an effective dose in dose titration for individual patients because of its clinical efficacy to a certain degree.

Recently, in order to pay attention to the voice of individual patients, Patient-Reported Outcome (PRO) has been often utilized in clinical trials, and the results are described in the product label for some products [14-15]. Although we did not collect data regarding the use of PRO in the clinical trials in the present study, the movement to utilize PRO including Patient-Reported Outcomes version of Common Terminology Criteria for Adverse Event (PRO-CTCAE) for the evaluation of AEs for antineoplastic agents [16] may contribute to optimal dose selection in the clinical development process [17].

The result of Research 2 indicated that, for "lower-dose prescription drugs," the medication was discontinued, reduced or suspended due to AEs in a fairly large proportion of subjects in their pivotal studies. This suggests a possibility of identifying products that should be actively monitored for clinical use in the post-marketing, even though the optimal dose was not identified by the time of approval. However, at the same time, we found few drugs among the no "lower-dose prescription drugs" that had high

proportion of patients whose medication was discontinued, reduced or suspended due to AEs, highlighting the difficulties in identifying drugs which might be used at lower dose in the post-marketing with a certain threshold.

There are some reports recommending the use of drugs at dosage lower than the approved dose for the elderly population or for reducing adverse effects [3-6]. We assumed that for "lower-dose prescription drugs" their recommended dose had been evaluated based on results of pivotal studies that lacked enough data in elderly patients. The result of Research 2, however, did not show the relationship between "lower-dose prescription drugs" and proportion of elderly patients in their pivotal studies, suggesting that prescription at lower dose to the elderly population alone does not account for the lower dose prescription in the post-marketing.

Prescription of drugs at a lower dose, unlike prescriptions of higher dose than the approved dose, is likely to be accepted as an optimization strategy for individual patients under a physician's discretion. However, if the optimal dose is different from the approved dose, it should be indicated in the product label and relevant information should be provided to ensure that anyone can use the drug at the optimal dose. In the present study, we observed some products for which over 90% of the prescriptions were out of the range of the approved dose. Thus, it is important to pay more attention to and monitor the actual dosage in the post-marketing phase, and to search the optimized recommended dosage, which is applicable to a greater number of patients without causing lack of efficacy.

In some Japanese product labels, dose for special populations are described in the section "Precautions concerning dosage and administration" and "Precautions concerning patients with specific backgrounds," which are clearly distinguished from the approved dose described in the section "Dosage and administration" [10]. As shown in Table 3, all

9 antineoplastic agents among the 27 “lower-dose prescription drugs” had the DSP (dose for special population) category, and for 2 products (Bosutinib and Vorinostat) among them, the proportion of prescriptions at doses lower than the DSP was over 30% in the database of either MDV or JammNet. In contrast, for non- antineoplastic agents, 5 products out of 18 had the DSP category and the proportion of prescriptions at doses lower than the DSP was not over 30%; however, the remaining 13 products did not have the DSP category. This may indicate that enough information on dose adjustment is not provided on the product label for non- antineoplastic agents.

As a countermeasure to bridge the gap between optimized dose and approved dose, we believe that the use of Real-World Data (RWD) would help to promptly deliver information on the optimized dose for each pharmaceutical product. Real-world evidence on the actual use of drugs would compensate the limited information obtained before approval [18, 19]. We can utilize RWD to identify lower-dose prescriptions with the patients’ background and plan post-marketing clinical trials to examine the benefit/risk balance of lower dose use for the specific populations, if necessary.

Limitation to the present study was that the information of individual patients’ background to whom lower doses of drugs were prescribed was not collected. In addition, the fact that parenteral preparations (e.g., injections and inhalations) were not included in the drugs examined was another limitation. We need to interpret the results with caution considering these limitations. Further studies are needed to clarify situations and backgrounds related to lower-dose prescriptions.

5 Conclusion

To the best of our knowledge, the present study is the first to elucidate the actual

situation of lower-dose prescriptions and the influencing factors thereon. The results suggest a limitations in determining a dose applicable to the majority of patients for various post-marketing usages, emphasizing the importance of reexamining the optimal dose, if necessary. We believe that the utilization of RWD could be of help in this regard.

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