Effect of the emergence of new drugs on the number of patients diagnosed

Toshiya Oka
DP-20401

Department of Clinical Medicine (Pharmaceutical Medicine)
Graduate School of Pharmaceutical Sciences
Kitasato University

5-9-1 Shirokane, Minato-ku, Tokyo, 108-8641, Japan

Abstract

For diseases with low awareness, such as rare diseases, the reported number of patients may be lower than the actual number of patients due to inaccurate epidemiological data. If a pharmaceutical company decides whether or not to develop a drug based on the business evaluation relying on the reported number of patients, the low reported number of patients may lead to a negative business evaluation, which may inhibit drug development.

The number of patients reported in epidemiological studies is based on the population of patients who meet the diagnostic criteria among those who visit medical institutions. The number of patients diagnosed can be affected by biological factors. It can also be affected by non-biological factors such as changes in diagnostic criteria and changes in disease awareness. In some diseases, reports have speculated a relationship between an increased number of diagnosed patients and a greater awareness of the disease. The emergence of new drugs may increase the number of diagnosed patients by affecting the patients' and physicians' awareness of the disease. The emergence of new drugs may bring new patients, who believe in the possibility of a cure, to medical institutions. As physicians become aware of new treatment opportunities with the emergence of new drugs, they may make more careful diagnoses, increasing the number of diagnosed patients. However, to my knowledge, there are no studies that investigated the effect of the emergence of new drugs on the number of patients diagnosed based on multiple disease data. Therefore, this research aimed to investigate the effect of the emergence of new drugs on the number of patients diagnosed. This research consisted of 3 parts. In research 1 and 2, effect of the emergence of new drugs on the number of patients diagnosed was investigated by using publicly available data on intractable diseases. In research 3, it was investigated whether

the results found in research 1 and 2 could apply to diseases with a higher number of patients than intractable diseases by using the publicly available data of the number of patients by the International Classification of Diseases 10th Revision code.

In research 1, the correlation between the change in the number of patients diagnosed and the number of drugs indicated, as well as factors such as the number of relevant scientific articles (as a potential indicator of disease awareness), and changes in diagnostic criteria and certification criteria were investigated. Also, the effect of the emergence of new drugs on the number of patients subsequently diagnosed was investigated by multivariate regression analyses. As a result of the correlation analysis, the rate of increase in the number of both drugs and articles was associated with the rate of increase in the number of patients diagnosed, regardless of changes in diagnostic criteria. The correlation coefficient of the increase rate of the number of drugs was higher than that of the increase in the number of drugs. This suggested that the effect of increased availability of drugs on the increase in the number of patients was larger for diseases that had fewer therapeutic drugs. The multivariate regression analyses demonstrated that the increased rate of the number of drugs available was a statistically significant factor that positively correlated with the rate of increase in the number of patients diagnosed in the following period. And the increase rate of the number of patients was not associated with the increase rate of the number of drugs in the following period. Considering these together, it was indicated that the increase in the number of drugs available could be one of the causes for the future increase in the number of patients diagnosed.

In research 2, it was investigated whether the number of patients diagnosed was changed after the emergence of new drugs at the level of individual diseases, and which type of drugs had a greater impact on the changes in the number of patients diagnosed. The annual

rate of increase in the number of patients was compared between before and after the emergence of new drugs. Factors affecting the annual rate of increase in the number of patients were investigated by simple linear regression analysis. As a result, the number of patients diagnosed increased after the emergence of new drugs at the level of individual diseases (Wilcoxon signed-rank test; $p = 0.035$). The simple linear regression analysis demonstrated that the emergence of drugs with new mechanisms of action was a statistically significant factor that was associated with an increase in the number of patients diagnosed. Four diseases had drugs with new mechanisms of action approved. These four diseases were associated with the greatest annual rate of increase in the number of patients diagnosed, suggesting that the emergence of drugs with new mechanisms of action had a greater effect on the annual rate of increase in the number of patients diagnosed.

In research 3, a descriptive analysis was performed for individual diseases to investigate the relationship between the trends in the number of patients and the emergence of new drugs. The diseases which met “more than 200,000 patients”, “disease code was the name of the disease”, and “low likelihood of mixing with other diseases and symptoms” etc. were selected. As a result, the findings from Alzheimer's disease suggested that the emergence of new drugs was associated with an increase in the number of patients subsequently diagnosed. Particularly, the emergence of drugs with new mechanisms of action in the absence of existing drugs was associated with a greater increase in the number of patients subsequently diagnosed.

From the results of research 1 to 3, the number of patients diagnosed increased after the emergence of new drugs, and this effect was considered to be larger for diseases that had fewer therapeutic drugs. And drugs with new mechanisms of action had a greater effect

on the increase in the number of patients diagnosed. Considering these together, it has been suggested that the higher the novelty of a new drug for a target disease, the greater the potential effect of the emergence of new drugs, as the novelty contributes to the increase in disease awareness among patients and physicians. As some potential patients are not evaluated using epidemiological data, the emergence of new drugs could increase the number of patients diagnosed by improving disease awareness among patients and physicians. Based on the above, I propose that pharmaceutical companies should consider that potential patients will come forward to receive treatment if new drugs are available in deliberating whether or not to develop new drugs for the diseases. This will help accelerate drug development, particularly in rare diseases.

Table of Contents

List of Tables

List of Figures

Abbreviations

Abbreviation	Definition
ADHD	Attention-deficit hyperactivity disorder
ICD-10	International Classification of Diseases 10th Revision
MHLW	Ministry of Health, Labor, and Welfare
MOA	Mechanisms of action
NAS	New active substance

1. Introduction

For diseases with low awareness, such as rare diseases, the reported number of patients may be lower than the actual number of patients due to inaccurate epidemiological data. Epidemiological data may not be reported for some rare diseases. If a pharmaceutical company decides whether or not to develop a drug based on the business evaluation relying on the reported number of patients, the low reported number of patients may lead to a negative business evaluation, which may inhibit drug development.

Disease prevalence is reported to be affected by several factors such as age, sex, comorbidities, and exercise according to epidemiological studies [1-3]. These factors are considered to be biologically or physiologically related to the incidence of various diseases. Another aspect of disease prevalence can be attributed to non-biological factors such as changes in diagnostic criteria and disease awareness. The number of patients reported in epidemiological studies is based on the population of patients who meet the diagnostic criteria among those who visit medical institutions. Therefore, patients who do not go to medical institutions are not counted, and the number of patients also fluctuates with changes in the diagnostic criteria. It is also possible that physicians overlook patients who would otherwise meet the diagnostic criteria. The process of patient visits and appropriate diagnoses may be influenced by the awareness of the disease among patients and physicians. In the areas of asthma [4], migraine [5], and anaphylaxis [6], reports have speculated a relationship between an increased incidence rate and a greater awareness of the disease.

The emergence of new drugs may have affected the patients' and physicians' awareness of the disease. For example, an increase in the number of drugs indicated to treat attention-deficit hyperactivity disorder (ADHD) may have affected the number of prescriptions for

ADHD drugs and could account for the increased number of patients diagnosed from the 1990s to the 2000s [7-8]. This relationship was considered to be bidirectional; as drug therapy increased, the diagnosis of ADHD also increased and vice versa [8]. The emergence of new drugs may bring new patients, who believe in the possibility of a cure, to medical institutions. As physicians become aware of new treatment opportunities with the emergence of new drugs, they may make more careful diagnoses, increasing the number of diagnosed patients. Therefore, the emergence of new drugs may increase the number of diagnosed patients. However, to my knowledge, there have been no studies that investigated the effect of the emergence of new drugs on the number of patients diagnosed based on multiple disease data.

There are publicly available data on the number of patients with intractable diseases in Japan. Their policy for intractable/rare diseases was initiated in 1972 by the Ministry of Health, Labor, and Welfare (MHLW) to promote elucidation of the etiology of intractable diseases and to provide financial assistance to patients in return for providing data for research use [9]. Among these intractable diseases, 45 diseases were consistent targets of the research project from the 2004 to 2013 fiscal year, and all data were available under the same conditions. Therefore, I aimed to investigate the effect of the emergence of new drugs on the number of patients diagnosed by using these data.

In research 1, the relationship between the change in the number of patients diagnosed and the number of drugs indicated, as well as factors such as the number of relevant scientific articles (as a potential indicator of disease awareness), diagnostic criteria, and certification criteria were investigated by using the data of intractable diseases. And the effect of the emergence of new drugs on the number of patients subsequently diagnosed was investigated by the multivariate regression analyses.

In research 2, it was investigated whether the number of patients diagnosed was changed after the emergence of new drugs at the level of individual diseases, and which type of drugs had a greater impact on the changes in the number of patients diagnosed by using the data of intractable diseases.

In research 3, it was investigated whether the results found in research 1 and 2 could apply to diseases with a higher number of patients than intractable diseases. There are publicly available data on the number of patients by the International Classification of Diseases 10th Revision (ICD-10) code in Japan. By using the data of the ICD-10 code, it was investigated by descriptive method whether the number of patients diagnosed was changed after the emergence of new drugs at the level of individual diseases with a higher number of patients than intractable diseases.

2. Research 1

2.1 Objectives

To investigate whether there are factors associated with the increase in the number of patients, the relationship between the increase rate of the number of patients and the increase rate of the number of drugs, along with the increase rate of the number of articles, changes in diagnostic and certification criteria, and background factors such as age, sex, etc. were investigated by using 45 intractable diseases data from 2004 to 2013.

2.2 Methods

2.2.1 Number of patients

The examination was performed on 45 intractable diseases from the research project by the MHLW (Table 1), as 45 diseases have been targets of the MHLW research project consistently from the 2004 to 2013 fiscal year. All data were available under the same conditions. Among 45 diseases, 12 were neurological/muscular diseases and 8 were immunological diseases. When a doctor diagnosed a patient, the disease would meet specific certification criteria, and a recipient certificate was issued for the patient to receive a medical expense subsidy. The number of recipient certificates was used as a marker of the number of patients in this research. Each year, the Japanese government reports a breakdown of these statistics by sex and age (https://www.e-stat.go.jp/stat-search/files?page=1&toukei=00450027&tstat=000001031469). From these data, the rate of increase in the number of patients diagnosed was calculated by dividing the number of patients in 2013 by that in 2004. The percentage of male patients, patients aged 60 years or older, and patients under the age of 20 years in 2004 were calculated.

2.2.2 Number of drugs

A search was conducted in September 2020 for the 45 diseases on the website of the Pharmaceuticals and Medical Devices Agency, where information on all approved drugs in Japan is available (https://www.pmda.go.jp/PmdaSearch/iyakuSearch/). Drugs with the disease name in the package insert were searched. Words for the search (name of the 45 diseases in Japanese) were determined after checking all Japanese notations of each disease, including words in the materials of the MHLW research project and the product package inserts. If the non-proprietary name was the same, it was counted as one drug even though there were multiple dosage strengths or forms for the drug. Generic drugs and biosimilar drugs were not counted. From these data, the increase in the number of drugs was calculated as the number of drugs approved from 2004 to 2013 fiscal year. The rate of increase in the number of drugs was calculated by dividing the cumulative number of drugs approved until 2013 fiscal year by that of 2003 fiscal year. In a disease for which the cumulative number of drugs approved until 2003 fiscal year was zero, one was added to both the numerator and denominator in the calculation of the increase rate.

2.2.3 Number of articles

A search was conducted for the 45 diseases on the Ichushi web in September 2020. The search targeted original articles, commentary articles, and review articles written in Japanese, and if it included the disease name in the title, it was counted as one. Words for the search were the same as those used in the search for the drugs. Based on the search result, the increase rate of the number of articles was calculated by dividing the cumulative number of articles published until 2013 calendar year by that of 2003 calendar year.

2.2.4 Diagnostic criteria

A search was conducted online for articles or reports on international or Japanese diagnostic criteria by academic societies or expert groups in the disease area to confirm the diagnostic criteria used in both 2004 and 2013 fiscal year. Then, the impact of the change in the diagnostic criteria from 2004 to 2013 on the number of patients was scored by five levels: -2, -1, 0, 1, and 2. The rules of scoring are shown in Table 2. This was used as the diagnostic criteria score.

2.2.5 Certification criteria

The use of certification criteria in the MHLW research project, both in the 2004 and 2013 fiscal years, was confirmed. Changes in the certification criteria from 2004 to 2013 were scored in the same manner as the diagnostic criteria. This was used as the certification criteria score.

2.2.6 Statistical analysis

Pearson's correlation coefficient was calculated, and the test for no correlation was performed between the increase rate of number of patients and each factor. For the factors that had a meaningful association with the increase in the number of patients, the partial correlation coefficient by Pearson's method was calculated between the increase rate and each factor, with the effect of the diagnostic criteria score or the certification criteria score removed, and tests for no partial correlation performed. In the test for no correlation and no partial correlation, statistical significance was defined as a p-value less than 0.05.

For factors that had a statistically significant partial correlation in the above analysis, linear regression analyses were performed. Regarding these factors plus the increase rate of the number of patients, data (2004–2013) mentioned above were divided into the first half (2004–2008) and the latter half (2009–2013), and the data of the latter half was used

as a dependent variable and data of the first half were used as independent variables. In the linear regression analysis, statistical significance was defined as a p-value less than 0.05. All the statistical analyses were performed using SAS Enterprise Guide 7.1.

Table 1. List of the intractable diseases and the new drugs in research 1

	Name of intractable diseases	Name of new drugs	Year of approval
1	Behcet's disease	Infliximab	2006
		Adalimumab	2013
2	Multiple sclerosis	Interferon beta-1a	2006
		Fingolimod	2011
		Methylprednisolone sodium succinate	2012
		Natalizumab	2013
3	Myasthenia gravis	Ciclosporin	2006
		Polyethylene glycol treated human normal immunoglobulin	2011
4	Systemic lupus erythematosus	Cyclophosphamide	2010
		Azathioprine	2011
5	Subacute myelo-optico-neuropathy (SMON)	-	-
6	Aplastic anemia	Rabbit anti-human thymocyte immunoglobulin	2008
7	Sarcoidosis	-	-
8	Amyotrophic lateral sclerosis	-	-
9	Scleroderma, Dermatomyositis, and Polymyositis	Polyethylene glycol treated human normal immunoglobulin	2010
		Cyclophosphamide	2010
		Azathioprine	2011
		Tacrolimus	2013

Table 1. List of the intractable diseases and the new drugs in research 1 (continued)

Name of intractable diseases		Name of new drugs	Year of approval
10	Idiopathic thrombocytopenic purpura	Eltrombopag olamine	2010
		Romiplostim	2010
		Lansoprazole	2010
		Omeprazole	2010
		Rabeprazole	2010
		Amoxicillin	2010
		Clarithromycin	2010
		Metronidazole	2010
		Esomeprazole	2011
11	Polyarteritis nodosa	Cyclophosphamide	2010
		Azathioprine	2011
		Rituximab	2013
12	Ulcerative colitis	Tacrolimus	2009
		Infliximab	2010
		Adalimumab	2013
13	Aortitis syndrome	Cyclophosphamide	2010
		Azathioprine	2011
14	Buerger's disease	-	-
15	Pemphigus	Freeze-dried polyethylene glycol treated human normal immunoglobulin	2008
16	Spinocerebellar ataxia	-	-
17	Crohn's disease	Azathioprine	2006
		Adalimumab	2010
18	Fulminant hepatic failure	-	-

Table 1. List of the intractable diseases and the new drugs in research 1 (continued)

Name of intractable diseases		Name of new drugs	Year of approval
19	Malignant rheumatoid arthritis	-	-
20	Parkinsonian disorder (Progressive supranuclear palsy, Corticobasal degeneration, Parkinson's disease)	Ropinirole	2006
		Entacapone	2006
		Zonisamide	2008
		Apomorphine	2011
		Rotigotine	2012
		Istradefylline	2012
		Ioflupane (^{123}I)	2013
21	Amyloidosis	Tafamidis meglumine	2013
22	Ossification of posterior longitudinal ligament	-	-
23	Huntington's disease	Tetrabenazine	2012
24	Moyamoya disease (Occlusive disease in circle of Willis)	-	-
25	Wegener's granulomatosis	Cyclophosphamide	2010
		Azathioprine	2011
		Rituximab	2013
26	Idiopathic dilated (congestive) cardiomyopathy	-	-
27	Multiple system atrophy (Striatonigral degeneration, Olivopontocerebellar atrophy, Shy-Drager syndrome)	-	-
28	Epidermolysis bullosa (junctional or dystrophic)	-	-
29	Pustular psoriasis	Infliximab	2009
30	Spinal stenosis	-	-
31	Primary biliary cirrhosis	-	-
32	Severe acute pancreatitis	-	-

Table 1. List of the intractable diseases and the new drugs in research 1 (continued)

Name of intractable diseases		Name of new drugs	Year of approval
33	Idiopathic necrosis in femur head	-	-
34	Mixed connective tissue disease	Cyclophosphamide	2010
		Azathioprine	2011
35	Primary immunodeficiency syndrome	-	-
36	Idiopathic interstitial pneumonia	Pirfenidone	2008
37	Pigmentary degeneration of the retina	-	-
38	Prion disease	-	-
39	Primary pulmonary hypertension	Epoprostenol	2004
		Bosentan	2005
		Sildenafil	2007
		Tadalafil	2009
		Ambrisentan	2010
		Treprostinil	2013
40	Neurofibromatosis	-	-
41	Subacute sclerosing panencephalitis	-	-
42	Budd-Chiari syndrome	-	-
43	Idiopathic chronic pulmonary thromboembolism (pulmonary hypertensive)	Riociguat	2013
44	Lysosomal storage disease (including Fabry's disease)	Laronidase	2006
		Agalsidase alfa	2006
		Idursulfase	2007
		Galsulfase	2007
		Miglustat	2011
45	Adrenoleukodystrophy	-	-

-: not applicable

Table 2. The scoring method about the impact of the change in the diagnostic/certification criteria on the number of patients over the study period

Score	Definition
2	Consolidation of different diseases
1	Decrease of symptoms required for diagnosis Increase of target symptoms for diagnosis Change of lab data criteria leading to an increase in the number of eligible patients Decrease in the number of diseases requiring differentiation (≥ 5)
0	No change No change of content (minor editorial change only) Not applicable to 2, 1, -1, -2
-1	Increase of symptoms required for diagnosis Decrease of target symptoms for diagnosis Change of lab data criteria leading to a decrease in the number of eligible patients Increase in the number of diseases requiring differentiation (≥ 5)
-2	Separation into different diseases

Note: Multiple items of 1 or -1 did not meet 2 or -2 (2 or -2 was selected only in case of meeting its definition). If there were multiple items of 1 or -1 coexisted, the score was selected from 1, 0, -1 based on the sum of items (sum of items: positive=1, zero=0, negative=-1).

2.3 Results

2.3.1 Overview of the data

The rate of increase in the number of patients with the 45 intractable diseases ranged from 0.72 to 3.50, and the mean was 1.57. In 40 diseases, the rate of increase in the number of patients was more than 1.00.

The information of new drugs per disease is shown in Table 1. Sixty-three new drugs were approved for 22 diseases during the target period; an average of 2.9 (range 1–9) new drugs were approved per disease. The rate of increase in the number of drugs with the 45 intractable diseases ranged from 1.00 to 7.00 (mean 1.41).

The rate of increase in the number of articles with the 45 intractable diseases ranged from 1.00 to 5.25 (mean 1.50).

2.3.2 Correlation coefficient with the increase rate of the number of patients

The correlation coefficient between the increase rate of patients and each factor, and the result of the test for no correlation are shown in Table 3. A statistically significant positive correlation was observed between the increase rate of the number of patients and that of the number of drugs (R=0.5528) and that of the number of articles (R=0.6033). Scatter plots of these two factors are shown in Figure 1. A statistically significant positive correlation was also observed in the increase in the number of drugs (R=0.2954) and the certification criteria score (R=0.3153), but the correlation coefficients were not high. The correlation coefficient of the increase in the number of drugs was lower than that of the increase rate of the number of drugs. Age, sex, baseline number of patients, baseline number of drugs, and diagnostic criteria were not associated with the increase rate of the number of patients.

2.3.3 Partial correlation coefficient with the increase rate of the number of patients

Both the increase rate of the number of drugs and the increase rate of the number of articles showed a statistically significant positive partial correlation with the increase rate of the number of patients, in the case when either the effect of diagnostic criteria score or certification criteria score was removed (Table 3).

2.3.4 Linear regression analysis

Regarding the three factors—increase rate of the number of patients, drugs, and articles—data (2004–2013) were divided into the first half (2004–2008) and the latter half (2009–2013). Linear regression analyses in which the latter half were a dependent variable and the first half were independent variables were performed. The result is shown in Table 4.

2.3.4.1 Increase rate of the number of patients (2009–2013) as a dependent variable

Adjusted R^2 was more than 0.65 in this analysis. A statistically significant beta coefficient was observed in the increase rate of the number of patients (2004–2008) and the increase rate of the number of drugs (2004–2008), which indicated that these two factors were correlated with the increase rate of the number of patients (2009–2013).

2.3.4.2 Increase rate of the number of drugs (2009–2013) as a dependent variable

Adjusted R^2 was low in this analysis, which indicated that no factor was associated with the increase rate of the number of drugs (2009–2013).

2.3.4.3 Increase rate of the number of articles (2009–2013) as a dependent variable

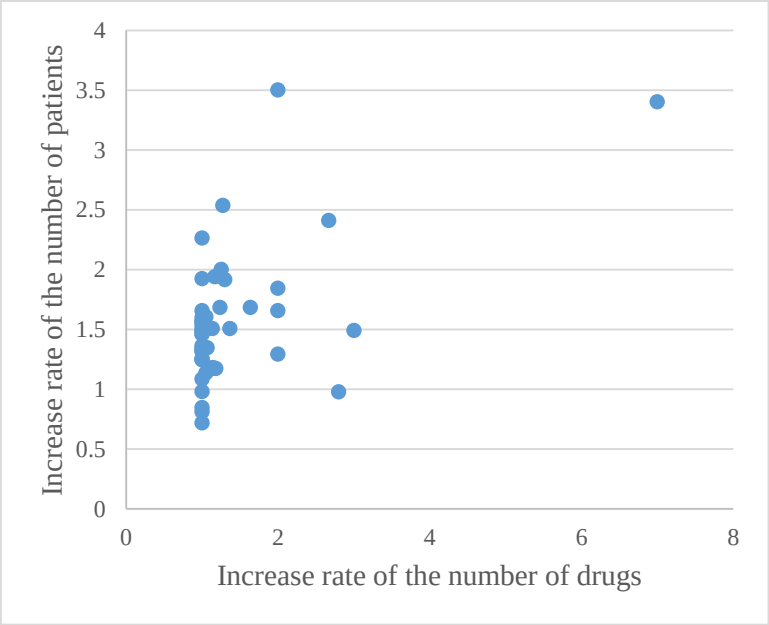
Adjusted R^2 was more than 0.65 in this analysis. A statistically significant beta coefficient was observed in the increase rate of the number of articles (2004–2008), which indicated that only the increase rate of the number of articles (2004–2008) was correlated with the increase rate of the number of articles (2009–2013).

Table 3. Correlation/Partial correlation coefficient with the increase rate of the number of patients

Factor	Correlation coefficient	Partial correlation coefficient
Increase rate of the number of drugs	0.5528**	0.5497** 0.5274**
Increase of the number of drugs	0.2954*	-
Increase rate of the number of articles	0.6033**	0.6003** 0.5742**
Diagnostic criteria score	-0.1446	-
Certification criteria score	0.3153*	-
Number of patients in 2004	-0.0613	-
% of the male in 2004	-0.0332	-
% of ≥ 60 years old in 2004	0.0345	-
% of < 20 years old in 2004	-0.1670	-
Cumulative number of drugs approved until 2003	-0.1602	-

Partial correlation coefficient: upper is the effect of diagnostic criteria score removed, and lower is the effect of the certification criteria score removed.

* p-value is < 0.05, ** p-value is < 0.01



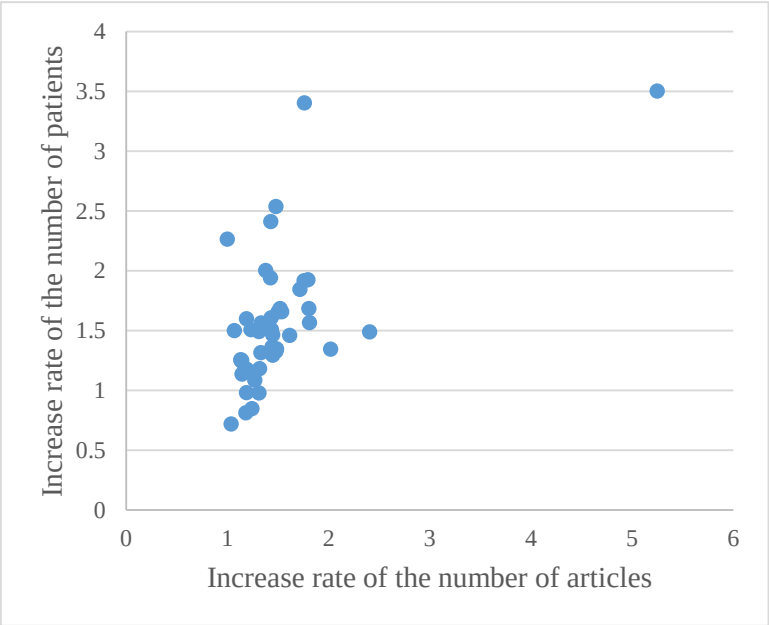


Figure 1. Scatter plots between the increase rate of the number of patients and each factor

Upper: increase rate of the number of drugs, lower: increase rate of the number of articles

Table 4. Result of the linear regression analysis

Dependent variable (2009-2013)	Increase rate of the number of patients	Increase rate of the number of drugs	Increase rate of the number of articles
Intercept	-0.041(0.158)	0.628(0.549)	-0.392(0.183)*
patients (2004-2008)	0.662(0.135)**	-0.073(0.469)	0.278(0.156)
drugs (2004-2008)	0.143(0.042)**	0.115(0.146)	-0.044(0.049)
articles (2004-2008)	0.249(0.126)	0.438(0.438)	1.075(0.146)**
R^2	0.679	0.046	0.682
Adjusted R^2	0.656	-0.024	0.659
F significance	< 0.01	> 0.05	< 0.01

Regression coefficient (Standard Error) was shown in each independent variable.

* p-value is < 0.05, ** p-value is < 0.01

2.4 Discussion

As both the increase rate of the number of patients and the increase rate of the number of drugs were statistically significant factors correlated with the increase rate of the number of patients diagnosed in the following period, and the increase rate of the number of patients was not associated with the increase rate of the number of drugs in the following period, it was suggested that the increase in the number of drugs available could be one of the causes for the future increase in the number of patients diagnosed.

The reasons the number of drugs correlated with the number of patients were considered as follows. First, the launch of new drugs could increase the chance of treatment for patients, resulting in more new patients visiting medical institutions. Second, increased opportunity for treatment by the new drug could improve the diagnostic environment and could raise the attention of physicians when they see potential patients, resulting in more diagnosis. The marketing efforts of pharmaceutical companies may also contribute to these 2 reasons by increasing disease awareness among patients and physicians. The number of patients diagnosed with a disease was based on diagnostic parameters, which included biomarkers and/or biological or physiological parameters that were closely related to the disease, and a drug was approved based on the changes in diagnostic parameters (efficacy). Therefore, this awareness might not be the same level of concept as the number of patients diagnosed with or drugs used for a disease. However, this possibility was supported by reports that speculated that increased awareness of diseases was associated with the increased incidence rate of the diseases [4-6]. These effects were indicated to be larger in the areas where there were fewer drugs because the correlation coefficient of the increase rate of the number of drugs was higher than that of the increase in the number of drugs.

The increase rate of the number of patients in the previous period was correlated with the increase rate of the number of patients in the following period, suggesting the existence of unmeasured biological or non-biological factors that affected the number of patients. Reasons why any factors did not contribute to the increased rate of the number of drugs were considered, and it was postulated that a 5-year period was not long enough for this assessment. This was mainly because it is difficult to develop new drugs in 5 years, and it might be due to other various factors that could affect drug development such as the business environment.

The disease composition of 45 intractable diseases might affect the findings of this research. Twelve were neurological/muscular diseases and 8 were immunological diseases. It might be relatively easy to conduct clinical trials on some neurological/muscular or immunological diseases for which pathogenesis was well-understood.

An association between the increase rate of the number of patients and the increase rate of the number of articles was found, but the reason for this association was not clear as the increase rate of the number of both patients and drugs were not associated with that of the number of articles in the linear regression analyses. Awareness of diseases might not be sufficiently increased by an increased number of articles. A larger number of patients could provide more opportunities for research, resulting in more articles, but this effect did not happen presumably because 45 intractable diseases were diseases with a relatively smaller population. Additionally, the number of researchers and amount of research funding might vary among studies for these 45 intractable diseases.

One of the limitations of this research was there were few approved drugs in the intractable disease area and research was less advanced. Therefore, the launch of new

drugs may have affected the increase rate of the number of patients compared to the therapeutic areas of more drugs. The second limitation was that the 45 intractable diseases all had relatively small populations. As such, it remains unknown whether these findings could also be applicable to diseases affecting a larger population. The third limitation was that data on the number of patients were obtained from a Japanese national research project. As such, whether these findings are applicable outside Japan remains unknown, although they may provide useful information for any country. The fourth limitation was that the number of patients within the study was based on the recipient certificates, so bias of physicians' willingness to diagnose to help potential patients economically could exist. From this viewpoint, the burden of drug costs could also be a potential bias; however, there has been a system in the national health insurance program in Japan, where a patient only pays capped medical expense when the cost is high. As the target of medical expense subsidy includes both drug and non-drug costs, there is an economic benefit for all the patients, and it was suggested that the target patients were diagnosed regardless of the number of drugs available. Due to this, any bias was considered insignificant. The fifth limitation was that patients could live longer for various reasons; however, it is unlikely that the survival improvement occurred only in the diseases with new drugs, and new drugs might not affect the survival significantly because not all 45 intractable diseases were life-threatening.

3 Research 2

3.1 Objectives

The results of research 1 indicated that the increase in the number of drugs available could be one of the causes for the future increase in the number of patients diagnosed. Further investigation on the effect of the emergence of new drugs on the number of patients diagnosed was performed at the level of individual diseases. In research 2, it was investigated whether the annual rate of increase in the number of patients diagnosed was changed after the emergence of new drugs at the level of individual diseases, focusing on the diseases which had new drugs from 2004 to 2013 among the 45 intractable diseases.

3.2 Methods

3.2.1 Number of patients and selection of target diseases

The data of the number of patients was the same as used in research 1. As the number of patients in 2 out of 47 prefectures in 2010 was not reported due to an earthquake, the number of patients in 2010 was corrected using the average ratio of the number of patients in two prefectures for each disease, calculated from the data for the remaining 9 years. Forty-five intractable diseases could be targeted for this research. In research 1, it was identified that new drugs were approved and became available for 22 out of the 45 diseases from the 2004 to 2013 fiscal year. Among the 22 diseases, target diseases were 18 diseases for which data for at least 2 years could be obtained before and after the emergence of the first new drug in the period from 2004 to 2013 (Table 5).

3.2.2 Average annual rate of increase in the number of patients

The average annual rate of increase (percentage) in the number of patients (= (the number of patients in this year/that of last year – 1) x 100) was calculated for the pre- and post-

periods. The pre- and post-periods were defined as the period before the fiscal year when the first new drug was approved for each disease and as the period after that, respectively. The duration of pre- and post-periods was the same within the same disease, and the maximum obtainable duration was used (Table 5). For example, assuming the first new drug for the disease was approved in 2006, the average of ((the number of patients in 2006/that of 2005 – 1) x 100) and ((the number of patients in 2005/that of 2004 – 1) x 100) would be the average annual rate of increase in the number of patients in the pre-period. The average of ((the number of patients in 2008/that of 2007 – 1) x 100) and ((the number of patients in 2007/that of 2006 – 1) x 100) would be the average annual rate of increase in the number of patients in the post-period.

3.2.3 Characteristics of the diseases

The percentage of patients aged less than 20 years, patients aged more than 60 years, and male patients in 2004 were calculated by the same way as research 1.

3.2.4 Characteristics of the new drugs

The data of the number of drugs was the same as used in research 1. Additionally, an investigation on the documents containing detailed information on each new drug (e.g. package insert, review report etc.) was performed. With reference to the above information, the drug was classified as a new active substance (NAS) if its active substance was approved for the first time in Japan and as a new mechanisms of action (MOA) if its active substance was an NAS and its MOA was novel in the disease.

3.2.5 Diagnostic and certification criteria

The data of both the diagnostic criteria score and certification criteria score were the same as used in research 1.

3.2.6 Statistical analysis

The comparison of the average annual rate of increase in the number of patients between the pre- and post-periods was performed using a Wilcoxon signed-rank test. Statistical significance was defined as a p-value less than 0.05. Simple linear regression analysis was performed with the difference between the pre- and post-periods, designating the average annual rate of increase in the number of patients with each disease as the dependent variable and the following factors as the independent variables: the fiscal year in which the first new drug was approved in the period from 2004 to 2013 (YEAR), the cumulative number of drugs approved until 2003, the number of drugs approved in the post-period, the presence or absence of NAS drugs approved in the YEAR, the presence or absence of new MOA drugs approved in the YEAR, the diagnostic criteria score, the certification criteria score, the number of patients in 2004, the percentage of patients aged less than 20 years in 2004, the percentage of patients aged more than 60 years in 2004, and the percentage of male patients in 2004. Statistical significance was defined as a p-value less than 0.05. All statistical analyses were performed using Microsoft Excel 2013.

Table 5. List of the intractable diseases and the new drugs in research 2

Name of intractable diseases		Name of new drugs	Year of approval	Applicability		Target Period	
				NAS	New MOA	Pre	Post
1	Behcet's disease	Infliximab	2006	-	-	2004-2006	2006-2008
2	Multiple sclerosis	Interferon beta-1a	2006	Yes	-	2004-2006	2006-2008
3	Myasthenia gravis	Ciclosporin	2006	-	-	2004-2006	2006-2008
4	Systemic lupus erythematosus	Cyclophosphamide	2010	-	-	2007-2010	2010-2013
		Azathioprine	2011	-	-		
6	Aplastic anemia	Rabbit anti-human thymocyte immunoglobulin	2008	Yes	Yes	2004-2008	2008-2012
9	Scleroderma, Dermatomyositis, and Polymyositis	Polyethylene glycol treated human normal immunoglobulin	2010	-	-	2007-2010	2010-2013
		Cyclophosphamide	2010	-	-		
		Azathioprine	2011	-	-		
		Tacrolimus	2013	-	-		
10	Idiopathic thrombocytopenic purpura	Eltrombopag olamine	2010	Yes	Yes	2007-2010	2010-2013
		Romiplostim	2010	Yes	Yes		
		Lansoprazole	2010	-	-		
		Omeprazole	2010	-	-		
		Rabeprazole	2010	-	-		
		Amoxicillin	2010	-	-		
		Clarithromycin	2010	-	-		
		Metronidazole	2010	-	-		
		Esomeprazole	2011	Yes	-		

Table 5. List of the intractable diseases and the new drugs in research 2 (continued)

Name of intractable diseases		Name of new drugs	Year of approval	Applicability		Target Period	
				NAS	New MOA	Pre	Post
11	Polyarteritis nodosa	Cyclophosphamide	2010	-	-	2007-2010	2010-2013
		Azathioprine	2011	-	-		
		Rituximab	2013	-	-		
12	Ulcerative colitis	Tacrolimus	2009	-	-	2005-2009	2009-2013
		Infliximab	2010	-	-		
		Adalimumab	2013	-	-		
13	Aortitis syndrome	Cyclophosphamide	2010	-	-	2007-2010	2010-2013
		Azathioprine	2011	-	-		
15	Pemphigus	Freeze-dried polyethylene glycol treated human normal immunoglobulin	2008	-	-	2004-2008	2008-2012
17	Crohn's disease	Azathioprine	2006	-	-	2004-2006	2006-2008
20	Parkinsonian disorder (Progressive supranuclear palsy, Corticobasal degeneration, Parkinson's disease)	Ropinirole	2006	Yes	-	2004-2006	2006-2008
		Entacapone	2006	Yes	-		
		Zonisamide	2008	-	-		
25	Wegener's granulomatosis	Cyclophosphamide	2010	-	-	2007-2010	2010-2013
		Azathioprine	2011	-	-		
		Rituximab	2013	-	-		
29	Pustular psoriasis	Infliximab	2009	-	-	2005-2009	2009-2013
34	Mixed connective tissue disease	Cyclophosphamide	2010	-	-	2007-2010	2010-2013
		Azathioprine	2011	-	-		
36	Idiopathic interstitial pneumonia	Pirfenidone	2008	Yes	Yes	2004-2008	2008-2012

Table 5. List of the intractable diseases and the new drugs in research 2 (continued)

Name of intractable diseases	Name of new drugs	Year of approval	Applicability		Target Period	
			NAS	New MOA	Pre	Post
44 Lysosomal storage disease (including Fabry's disease)	Laronidase	2006	Yes	Yes	2004-2006	2006-2008
	Agalsidase alfa	2006	Yes	-		
	Idursulfase	2007	Yes	Yes		
	Galsulfase	2007	Yes	Yes		

MOA: mechanisms of action, NAS: new active substance, -: not applicable

3.3 Results

3.3.1 Overview of new drugs approved during the target period

The information of new drugs, NAS drugs, and new MOA drugs per disease is shown in Table 5. Forty-three new drugs were approved for 18 diseases during the target period; an average of 2.4 (range 1–9) new drugs were approved per disease during the target period. Twelve NAS drugs were approved for six diseases during the target period; an average of 2 (range 1–4) NAS drugs were approved per disease during the target period. Seven new MOA drugs were approved for four diseases during the target period; an average of 1.8 (range 1–3) new MOA drugs were approved per disease during the target period. Thirty-one of the 43 new drugs, excluding 12 NAS drugs, were new drugs approved for expanded indications.

3.3.2 Comparison of the annual rate of increase in the number of patients between the pre- and post-periods

The average annual rate of increase in the number of patients in the pre- and post-periods is shown in Figure 2 and Table 6. The annual rate of increase in the number of patients in the post-period was significantly higher than that in the pre-period (Wilcoxon signed-rank test; $p = 0.035$). The mean increase from pre- to post-period for 18 diseases was 0.9% per year. Four diseases had new MOA drugs approved: pirfenidone for idiopathic interstitial pneumonia, laronidase for lysosomal storage disease, eltrombopag olamine and romiplostim for idiopathic thrombocytopenic purpura, and rabbit anti-human thymocyte immunoglobulin for aplastic anemia. These four diseases were the top four diseases for which the annual rate of increase in the number of patients in the post-period increased (Table 6). As the annual rate of increase in the number of patients in the pre-period for these four diseases was ranged from low to high in the group universally, the annual rate

of increase in the number of patients in the post-period for these four diseases increased irrespective of the trend in the pre-period (Figure 2).

3.3.3 Simple linear regression analysis

The results of the simple linear regression analysis and the data for the factors are shown in Table 6. Statistical significance was observed in the presence of NAS drugs, the presence of new MOA drugs, and the percentage of patients < 20 years old in 2004. Because the percentage of patients ≥ 60 years old in 2004 was not a statistically significant factor, the effect of age was not consistent in this analysis. Other factors including diagnostic criteria and certification criteria scores were not statistically significant.

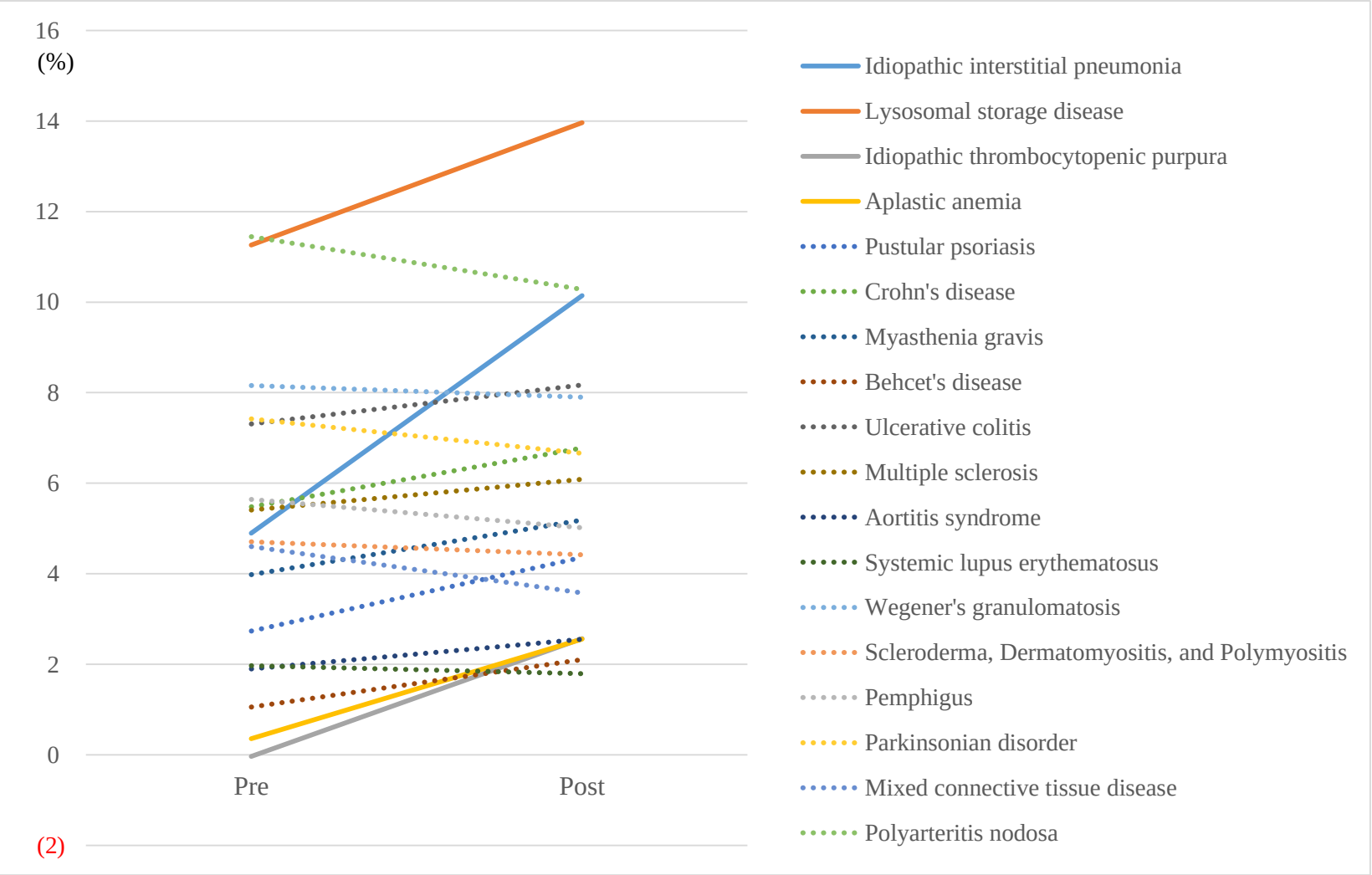


Figure 2. The annual rate of increase in the number of patients for each disease before and after the emergence of new drugs

Solid lines are diseases with new MOA drugs approved, and dotted lines are other diseases.

Table 6. Result of the simple linear regression analysis

Disease	The annual rate of increase in the number of patients (%)			YEAR	No. drugs by 2003	No. new drugs	NAS drug /Yes=1	New MOA drug /Yes=1	Diagnostic criteria	Certification criteria	No. patients in 2004	% <20 y.o.in 2004	% ≥60 y.o.in 2004	% male in 2004
	Pre	Post	Difference											
Idiopathic interstitial pneumonia	4.9	10.1	5.2	2008	0	1	1	1	-1	0	4176	0.5	83.9	8.1
Lysosomal storage disease	11.3	14.0	2.7	2006	3	4	1	1	0	0	401	9.5	10.7	47.8
Idiopathic thrombocytopenic purpura	0.0	2.6	2.6	2010	5	9	1	1	0	0	25545	9.6	44.9	43.2
Aplastic anemia	0.4	2.6	2.2	2008	20	1	1	1	0	0	9173	7.7	49.7	69.5
Pustular psoriasis	2.7	4.4	1.6	2009	15	1	0	0	1	1	1439	2.9	36.3	39.4
Crohn's disease	5.5	6.8	1.3	2006	2	1	0	0	0	0	23100	4.4	7.7	18.3
Myasthenia gravis	4.0	5.2	1.2	2006	15	1	0	0	0	0	13735	3.8	46.7	30.0
Behcet's disease	1.1	2.1	1.1	2006	14	1	0	0	0	1	16294	0.9	37.5	63.1
Ulcerative colitis	7.3	8.2	0.9	2009	18	3	0	0	0	0	79897	3.4	21.6	41.1
Multiple sclerosis	5.4	6.1	0.7	2006	17	1	1	0	0	1	10746	3.3	20.2	50.6
Aortitis syndrome	1.9	2.6	0.7	2010	11	2	0	0	0	1	5203	1.7	37.1	29.7
Systemic lupus erythematosus	2.0	1.8	-0.2	2010	14	2	0	0	0	1	52139	2.7	23.4	52.5
Wegener's granulomatosis	8.2	7.9	-0.3	2010	10	3	0	0	0	0	1135	1.1	47.2	40.3

Table 6. Result of the simple linear regression analysis (continued)

Disease	The annual rate of increase in the number of patients (%)			YEAR	No. drugs by 2003	No. new drugs	NAS drug /Yes=1	New MOA drug /Yes=1	Diagnostic criteria	Certification criteria	No. patients in 2004	% <20 y.o.in 2004	% ≥60 y.o.in 2004	% male in 2004
	Pre	Post	Difference											
Scleroderma, dermatomyositis, and polymyositis	4.7	4.4	-0.3	2010	11	4	0	0	0	1	32944	1.3	55.9	33.2
Pemphigus	5.6	5.0	-0.6	2008	21	1	0	0	0	0	3486	0.2	55.7	8.7
Parkinsonian disorder	7.4	6.7	-0.8	2006	11	3	1	0	-1	1	74928	0.0	91.3	10.2
Mixed connective tissue disease	4.6	3.6	-1.0	2010	0	2	0	0	0	0	7061	1.6	29.8	42.1
Polyarteritis nodosa	11.4	10.3	-1.2	2010	11	3	0	0	0	0	4209	0.6	65.4	62.5
Average			0.9											
			p-value	0.297	0.200	0.833	0.017	0.000	0.492	0.330	0.358	0.040	0.997	0.706

MOA: mechanisms of action, NAS: new active substance, No.: the number of, YEAR: the fiscal year when the first new drug was approved, y.o.: years old

3.4 Discussion

The result of the comparison of the annual rate of increase in the number of patients between the pre- and post-periods indicated that the number of patients diagnosed increased after the emergence of new drugs. This result indicated the effect of the emergence of new drugs in terms of changes in the number of patients with individual diseases. This result was consistent with that of research 1 which found that the increased rate of the number of drugs available was a statistically significant factor in multivariate regression analysis that positively correlated with the rate of increase in the number of patients diagnosed in the following period.

The results of simple linear regression analysis indicated that the emergence of new drugs, especially NAS drugs and drugs with a new MOA, was associated with an increase in the number of patients diagnosed. Four diseases had new MOA drugs approved. These four diseases were the top four diseases for which the annual rate of increase in the number of patients in the post-period was positive, suggesting that the new MOA drugs had a greater effect on the annual rate of increase in the number of patients.

New MOA drugs are novel agents for which no equivalent drugs are available. The result of research 1 indicated that the effect of increased availability of drugs on the increase in the number of patients was larger for diseases that had fewer therapeutic drugs. Therefore, it has been suggested that the higher the novelty of a new drug for a target disease, the greater the potential effect of the emergence of new drugs, as the novelty contributes to the increase in disease awareness.

As described in the discussion part of research 1, there are some reasons for the impact of new drugs on the increased awareness of relevant diseases, resulting in increased diagnoses. In addition, the marketing efforts of pharmaceutical companies may increase

awareness of the diseases among patients and physicians, particularly in the case of new MOA drugs.

Twelve were neurological/muscular diseases and 8 were immunological diseases in the 45 intractable diseases targeted in research 1. This disease composition might affect the findings in research 1 as it might be relatively easy to conduct clinical trials on some neurological/muscular or immunological diseases for which pathogenesis was well-understood. However, 3 of the top 4 diseases in which the annual rate of increase in the number of patients in the post-period was positive were neither neurological/muscular nor immunological diseases. Therefore, the effect of the emergence of new drugs could be observed regardless of the type of disease.

There are other limitations related to the use of the intractable disease data as written in the discussion part of research 1.

4 Research 3

4.1 Objectives

It was found that the increased rate of the number of drugs available was a statistically significant factor in the multivariate regression analysis that was positively correlated with the rate of increase in the number of patients diagnosed in the following period in research 1. Also, it was found that the number of patients diagnosed increased after the emergence of new drugs at the level of individual diseases, and new MOA drugs had a greater effect on the increase in the number of patients diagnosed in research 2.

These findings were based on the analyses from the data of 45 intractable diseases, which had relatively small populations. Therefore, it remains unknown whether the same result could be applied to diseases with a higher number of patients. Consequently, diseases with a higher number of patients than intractable diseases were targeted in research 3. There are publicly available data on the number of patients by ICD-10 code in Japan. Using these data, the relationship between the trends in the number of patients diagnosed and the emergence of new drugs indicated for the diseases with a higher number of patients than intractable diseases was investigated by a descriptive method.

4.2 Methods

4.2.1 Number of patients

The Japanese government reports a breakdown of the number of patients by sex, age, and disease code (ICD-10) every 3 years (https://www.e-stat.go.jp/stat-search/files?page=1&toukei=00450022&tstat=000001031167). The data from the 1996 to 2017 fiscal year were publicly available under the same conditions. As the number of patients in 2011 did not include the data for 2 prefectures due to an earthquake, the number

of patients in 2011 was corrected using the ratio of population in the 2 prefectures and that in the 47 prefectures in 2011.

4.2.2 Selection of target diseases

Diseases meeting all of the following five criteria were targeted: 1) more than 200,000 patients in either of the target fiscal years, 2) disease code was the name of the disease (neither symptom nor injury site), 3) disease code was consistent through the target period (minor editorial change was allowed), 4) low likelihood of mixing with other diseases and symptoms, 5) periods of both with and without the emergence of new drugs existed for at least 3 years.

4.2.3 Characteristics of the new drugs

The number of drugs indicated for each disease was investigated in the same way as research 1 in August 2022. Words for the search (name of the diseases in Japanese) were determined after checking all Japanese notations of each disease, including words in the product package inserts. The characteristics of the new drugs whether they were NAS drugs or new MOA drugs were investigated in the same way as research 2.

4.2.4 Descriptive analysis

Data of the number of patients for each disease from 1996 to 2017 fiscal years were used to graph the trends in the number of patients and the increase rate in the number of patients from the previous survey year (= (the number of patients in the target year/that of the previous survey year – 1) x 100). Information of the characteristics of new drugs from 1996 to 2017 fiscal year (number of new drugs, year of approval, and type of new drugs) were added to the graphs. Descriptive analyses were performed for each disease to investigate the relationship between the trends in the number of patients and the emergence of new drugs based on these graphs.

4.3 Results

4.3.1 Result of the selection of target diseases

Diseases that met all the selection criteria were Alzheimer's disease and hepatitis C.

4.3.2 The new drugs for each disease

The list of new drugs for Alzheimer's disease and hepatitis C is shown in Table 7.

Table 7. List of the diseases and the new drugs in research 3

Name of intractable diseases	Name of new drugs	Year of approval	Applicability	
			NAS	New MOA
1 Alzheimer's disease	Donepezil	1999	Yes	Yes
	Memantine	2010	Yes	Yes
	Galantamine	2010	Yes	-
	Rivastigmine	2011	Yes	-
	Florbetapir (^{18}F)	2016	Yes	-
	Flutemetamol (^{18}F)	2017	Yes	-
2 Hepatitis C	Ribavirin	2001	-	-
	Peginterferon alfa-2a	2003	Yes	-
	Peginterferon alfa-2b	2004	-	-
	Ursodeoxycholic Acid	2006	-	-
	Telaprevir	2011	Yes	Yes
	Simeprevir	2013	Yes	-
	Daclatasvir	2014	Yes	Yes
	Sofosbuvir	2014	Yes	Yes
	Asunaprevir	2014	Yes	-
	Vaniprevir	2014	Yes	-
	Ledipasvir and Sofosbuvir	2015	Yes	-
	Ombitasvir, Paritaprevir and Ritonavir	2015	Yes	-
	Elbasvir	2016	Yes	-
	Grazoprevir	2016	Yes	-
	Daclatasvir, Asunaprevir and Beclabuvir	2016	Yes	-
	Glecaprevir and Pibrentasvir	2017	Yes	-

MOA: mechanisms of action, NAS: new active substance, -: not applicable

4.3.3 Alzheimer's disease

The trends in the number of patients and the emergence of new drugs from 1996 to 2017 in Alzheimer’s disease were graphed (Figure 3).

There were no drugs approved for Alzheimer’s disease before 1996. One new MOA drug (Donepezil; Acetylcholinesterase inhibitor) was approved in 1999. One new MOA drug (Memantine; N-methyl-D-aspartate receptor antagonist) and one NAS drug (Galantamine; Acetylcholinesterase inhibitor) were approved in 2010. One NAS drug (Rivastigmine; Acetylcholinesterase inhibitor) was approved in 2011. Two NAS drugs (Florbetapir (^{18}F), Flutemetamol (^{18}F); Radiopharmaceutical for positron emission tomography) were approved in 2016 and 2017, respectively.

In the absence of existing drugs, the new MOA drug was approved in 1999. Since then, the number of patients continued to rise until 2017. New MOA drugs were approved in 1999 and 2010, and in both cases, the increase rate in the number of patients in 3 years following the emergence of the new MOA drug was higher than that before the emergence of the new MOA drug (2002/1999 versus 1999/1996 and 2011/2008 versus 2008/2005, respectively). Particularly, the increase rate in the number of patients from 1999 to 2002 was greater than that from 1996 to 1999. This case was the first appearance of the new drug in the absence of existing drugs.

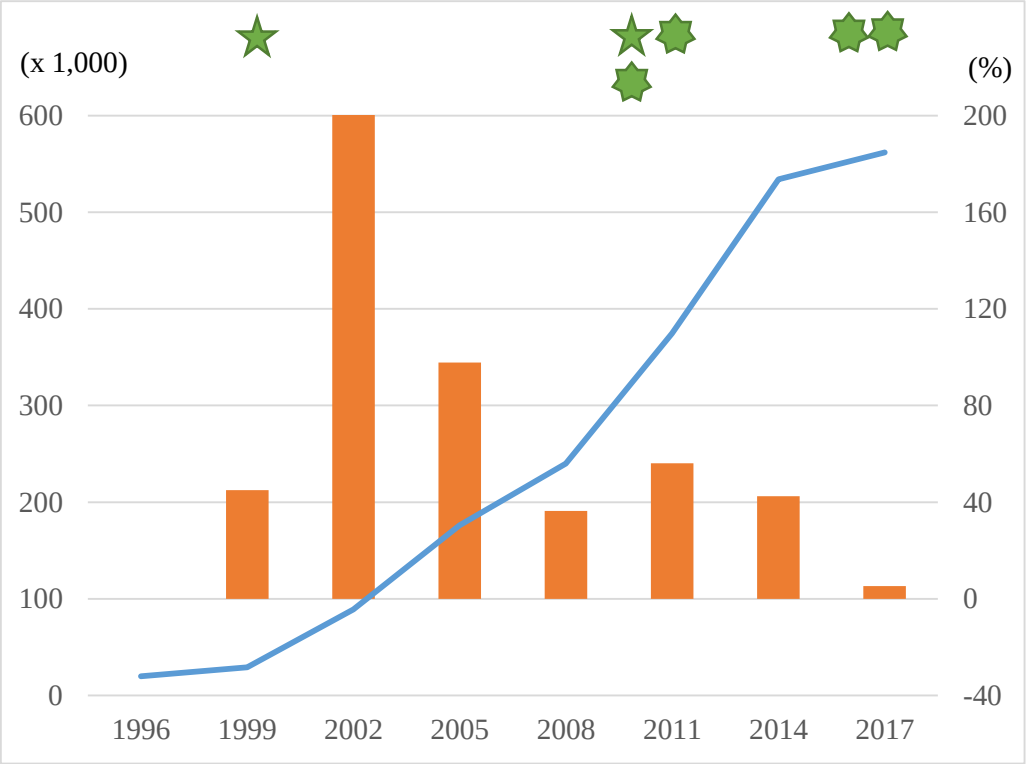


Figure 3. Trends in the number of patients and the emergence of new drugs (Alzheimer's disease)

Left axis: the number of patients (line), Right axis: the increase rate in the number of patients from the previous survey year (bars). ★ New MOA drug, ✹ NAS drug, ● New drug other than new MOA or NAS drug.

4.3.4 Hepatitis C

The trends in the number of patients and the emergence of new drugs from 1996 to 2017 in Hepatitis C were graphed (Figure 4).

There were 2 drugs (both Interferon-gamma) approved for Hepatitis C until 1996. One NAS drug (Pegylated interferon-gamma) and 3 new drugs (neither new MOA nor NAS drugs) (Pegylated interferon-gamma, Antiviral and Hepatoprotective drug) were approved from 2001 to 2006. Three new MOA drugs and 9 NAS drugs were approved from 2011 to 2017, and these 12 new drugs were all direct acting antivirals.

A new drug (neither new MOA nor NAS drug) was approved in 2001, and in this case, the increase rate in the number of patients in 3 years following the emergence of the new drug was higher than that before the emergence of the new drug (2002/1999 versus 1999/1996). However, after 2005, the number of patients continued to fall until 2017 despite the continued approval of new drugs during this period.

Hepatitis C had the following characteristics that distinguished it from other diseases. Hepatitis C was discovered in 1989 [10-11]. The main transmission route of Hepatitis C was blood transmission. Since the discovery of Hepatitis C, as antibody screening of blood for transfusion became available, new infections due to blood transfusions were considered to have decreased in Japan. And, Hepatitis C was considered to become curable due to the advances in drug treatments. Therefore, it was considered that the number of patients increased only for a certain period after the emergence of new drug (1999 to 2002); however, since then, the number of patients decreased as a result of the cure of the disease by new drugs.

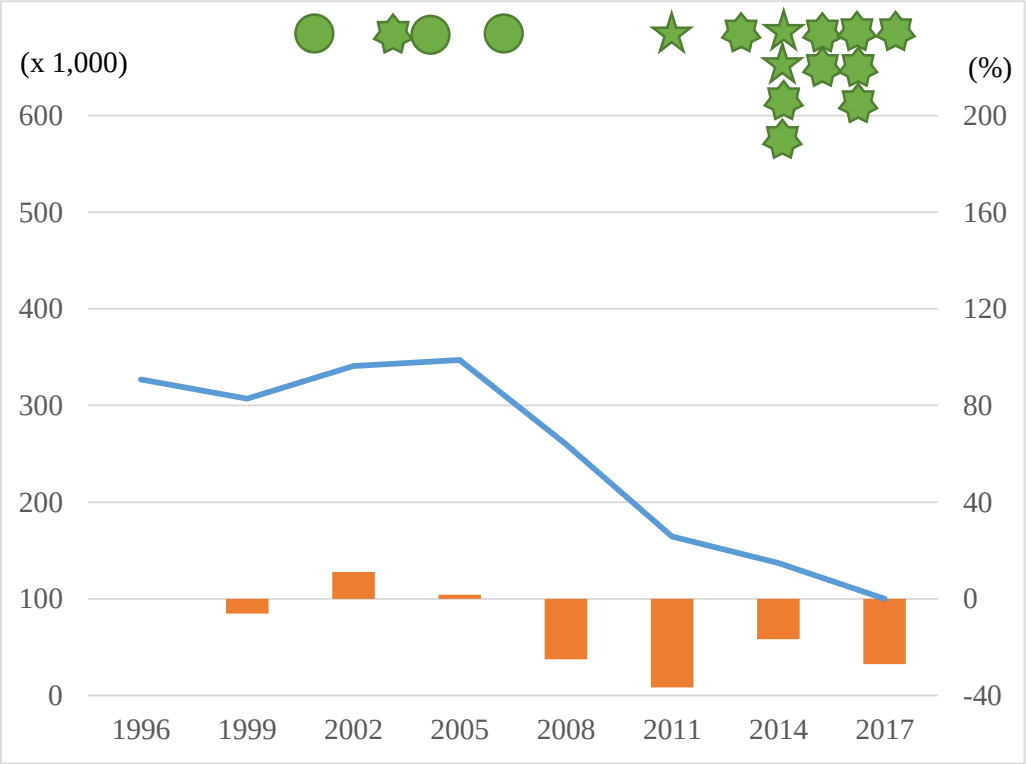


Figure 4. Trends in the number of patients and the emergence of new drugs (Hepatitis C)

Left axis: the number of patients (line), Right axis: the increase rate in the number of patients from the previous survey year (bars). ★ New MOA drug, NAS drug, New drug other than new MOA or NAS drug.

4.4 Discussion

The findings from Alzheimer's disease suggested that the emergence of new drugs was associated with an increase in the number of patients in the following period. Particularly, the emergence of new MOA drugs in the absence of existing drugs was associated with a greater increase in the number of patients in the following period. In research 1, it was found that the effect of increased availability of drugs on the increase in the number of patients was larger for diseases that had fewer therapeutic drugs. In research 2, it was found that new MOA drugs had a greater effect on the increase in the number of patients. The findings from Alzheimer's disease suggested consistent contents with these findings. In Hepatitis C, there was a period when the number of patients increased after the emergence of new drug. However, overall, the number of patients continued to fall despite the continued approval of new drugs. This may be due to the special circumstances of Hepatitis C, in which new infections have been suppressed and new drugs have developed to cure the disease.

It should be noted that the number of patients in research 3 was not the number of patients firmly diagnosed by diagnostic criteria even though it was counted by the disease code (ICD-10).

There were findings that suggested the emergence of new drugs was associated with the increase in the number of patients subsequently diagnosed for the diseases with a higher number of patients than intractable diseases. And, there were findings that suggested the emergence of new MOA drugs in the absence of existing drugs was associated with a greater increase in the number of patients diagnosed in the following period. However, it should be noted that the generalizability of these findings is limited due to the small sample size.

5. Overall Discussion and Conclusion

The investigation of data on 45 intractable diseases indicated that the rate of increase in the number of both drugs and articles was associated with the rate of increase in the number of patients diagnosed, regardless of changes in diagnostic criteria. The multivariate regression analyses demonstrated that the increased rate of the number of drugs available was a statistically significant factor that positively correlated with the rate of increase in the number of patients diagnosed in the following period. The investigation of data on 18 intractable diseases demonstrated that the number of patients diagnosed increased after the emergence of new drugs at the level of individual diseases and new MOA drugs had a greater effect on the increase in the number of patients diagnosed.

New MOA drugs are novel agents for which no equivalent drugs are available. Considering together with the finding that the effect of increased availability of drugs on the increase in the number of patients was larger for diseases that had fewer therapeutic drugs, it has been suggested that the higher the novelty of a new drug for a target disease, the greater the potential effect of the emergence of new drugs, as the novelty contributes to the increase in disease awareness among patients and physicians. Some potential patients are not evaluated using epidemiological data, particularly in rare diseases such as intractable diseases. Therefore, the emergence of new drugs could increase the number of patients diagnosed by improving disease awareness among patients and physicians.

In the investigation which was conducted using data on the diseases with a higher number of patients than intractable diseases, the findings from Alzheimer's disease suggested that the emergence of new drugs was associated with an increase in the number of patients diagnosed in the following period. Also, it was suggested that the emergence of new MOA drugs in the absence of existing drugs was associated with a greater increase in the number

of patients diagnosed in the following period. However, it should be noted that the generalizability of these findings is limited due to the small sample size.

Based on the above, I propose that pharmaceutical companies should consider that potential patients will come forward to receive treatment if new drugs are available in deliberating whether or not to develop new drugs for the diseases. This will help accelerate drug development, particularly in rare diseases.

References

1. Ninomiya T. Japanese Legacy Cohort Studies: The Hisayama Study. J Epidemiol. 2018;28(11):444-451.

2. Chen G, Levy D. Contributions of the Framingham Heart Study to the Epidemiology of Coronary Heart Disease. JAMA Cardiol. 2016;1(7):825-830.

3. Hersi M, Irvine B, Gupta P, Gomes J, Birkett N, Krewski D. Risk factors associated with the onset and progression of Alzheimer's disease: A systematic review of the evidence. Neurotoxicology. 2017;61:143-187.

4. Lundbäck B, Rönmark E, Jönsson E, Larsson K, Sandström T. Incidence of physician-diagnosed asthma in adults-a real incidence or a result of increased awareness? Report from The Obstructive Lung Disease in Northern Sweden Studies. Respir Med. 2001;95(8):685-92.

5. Lipton RB, Scher AI, Kolodner K, Liberman J, Steiner TJ, Stewart WF. Migraine in the United States: epidemiology and patterns of health care use. Neurology. 2002;58(6):885-94.

6. Turner PJ, Gowland MH, Sharma V, Ierodiakonou D, Harper N, Garcez T, et al. Increase in anaphylaxis-related hospitalizations but no increase in fatalities: an analysis of United Kingdom national anaphylaxis data, 1992-2012. J Allergy Clin Immunol. 2015;135(4):956-63.

7. Winterstein AG, Gerhard T, Shuster J, Zito J, Johnson M, Liu H et al. Utilization of pharmacologic treatment in youths with attention deficit/hyperactivity disorder in Medicaid database. Ann Pharmacother. 2008;42(1):24-31.

8. Olfson M, Blanco C, Wang S, Laje G, Correll CU. National trends in the mental health care of children, adolescents, and adults by office-based physicians. JAMA Psychiatry.

2014;71(1):81-90.

9. Kanatani Y, Tomita N, Sato Y, Eto A, Omoe H, Mizushima H. National Registry of Designated Intractable Diseases in Japan: Present Status and Future Prospects. Neurol Med Chir (Tokyo). 2017;57(1):1-7.

10. Choo QL, Kuo G, Weiner AJ, Overby LR, Bradley DW, Houghton M. Isolation of a cDNA clone derived from a blood-borne non-A, non-B viral hepatitis genome. Science. 1989;244(4902):359-62.

11. Kuo G, Choo QL, Alter HJ, Gitnick GL, Redeker AG, Purcell RH, et al. An assay for circulating antibodies to a major etiologic virus of human non-A, non-B hepatitis. Science. 1989;244(4902):362-4.

Acknowledgments

First and foremost, I would like to express my sincere gratitude to Professor Mamoru Narukawa for his thoughtful advice, knowledge, and guidance on my research.

I would like to thank all my colleagues at the Department of Clinical Medicine (Pharmaceutical Medicine), Graduate School of Pharmaceutical Sciences, Kitasato University for their thoughtful advice, warm encouragement, and support throughout my Ph.D. course.

I would also like to express my gratitude to Professor Yuji Yoshiyama, Professor Nobuhiko Okada, and Professor Yusuke Suzuki for their reviews and helpful discussion on this study.

Finally but certainly not least, I am extremely grateful to my family for their understanding, support, and warm encouragement throughout my Ph.D. course.