

ORIGINAL ARTICLE

Prevalence, treatments and medical cost of multiple sclerosis in Japan based on analysis of a health insurance claims database

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Keywords

claims database; disease-modifying therapy; health economics; multiple sclerosis; prevalence

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Abstract

Objective To understand, through an analysis of health insurance claims data, the current treatment status and medical cost of multiple sclerosis (MS) in Japan.

Methods We analyzed claims data (January 2005–January 2016) from the Japan Medical Data Center Co., Ltd., identifying MS patients, except those with neuromyelitis optica, using an algorithm based on diagnosis codes. Prescription drug usage and medical costs for MS patients were analyzed.

Results A total of 713 MS patients were identified in the database. Between 2011 and 2015, the age-adjusted prevalence of MS in the database increased from 0.015% to 0.019%, and the female-to-male ratio increased from 1.70 to 2.03. The prescription rate for disease-modifying therapy drugs was higher in larger care settings. Prescriptions for fingolimod increased from 2011, with a concomitant decrease in prescriptions for interferon. The per patient per month cost for MS was ¥124 337 (US\$1190 or €1084, as of October 2016). This was higher than the costs for Parkinson's disease (¥84 410), myasthenia gravis (¥82 944) and rheumatoid arthritis (¥53 843). However, the total per member per month cost for MS, which represents the population-based economic impact, was ¥25.2, which was lower than the parallel costs for Parkinson's disease (¥123.0) and rheumatoid arthritis (¥311.6) because of the low prevalence of MS in Japan.

Conclusions Using real-world data, we obtained up-to-date prevalence, treatment status and medical cost information for MS in Japan. The present results showed the efficacy of a real-world database to obtain the latest national trends for rare diseases, such as MS; this could have important implications for clinicians and policymakers.

Introduction

Multiple sclerosis (MS) is a chronic, autoimmune demyelinating disease of the central nervous system, which causes lifetime physical disability.¹ It is one of the most common neurological diseases, and is a leading cause of non-traumatic disability among young adults in the USA and Europe.² Disease-modifying therapies (DMT) are costly treatments used to prevent relapse for certain types of MS.³ Since the approval of the first DMT in the USA and Europe in

1993, medical costs for MS have rapidly increased, and now have a significant economic impact in these countries.⁴

The prevalence of MS in Japan is relatively low compared with that in the USA and Europe. To date, four nationwide surveys have been carried out in Japan, in 1972, 1982, 1989 and 2004; these were based on random samples of patients from hospitals throughout Japan.^{5,6} The 2004 survey was carried out by the Research Committees of Epidemiology of Intractable Diseases and Neuroimmunological

Diseases. A few other studies have reported the prevalence of MS in the northern part of Japan.^{7,8} Together with the reported numbers of recipient certificates for specific disease treatments,⁹ these studies show that the number of MS patients in Japan has been steadily increasing in recent years. It is therefore important for clinicians as well as policymakers to obtain up-to-date, nationwide information about trends in treatment status and medical costs for MS in Japan. In addition, at the time of the previous survey, optic-spinal MS, which is now considered to be a subcategory of neuromyelitis optica (NMO), was included within the definition of MS patients. Although diagnostic criteria of NMO was established in 2006,¹⁰ NMO is still included in the publicly available number of MS patients certified as specific disease by the Ministry of Health, Labor and Welfare in Japan.⁹ Therefore, there is little information about the nationwide prevalence and its transition of MS, not including NMO, in Japan.

Recently, data gathered from clinical practice, such as from hospital records and health insurance claims, have become increasingly available; these are referred to as “real-world data.”¹¹ We previously analyzed the medical costs of MS in Japan using the database of Medical Data Vision, one of the private companies accumulating data from hospitals that have adopted the Diagnosis Procedure Combination/Per-Diem Payment System.¹² This database system contained 10.5 million claims from 192 diagnosis procedure combination hospitals in Japan, enabling us to effectively analyze the data from a large number of MS patients. Using this database, we showed that the medical cost per patient per month (PPPM) for MS was approximately ¥94 000, which was 3.7-fold higher than the mean cost PPPM for the general population in Japan.¹² We also showed that the cost of DMT accounted for the largest component of the total medical cost, especially for patients under the age of 50 years.¹² These data, together with the increase in the number of MS patients in Japan, suggested that the economic impact of MS, most of which was attributable to DMT, was also growing in Japan. However, as Medical Data Vision’s database did not contain population data, we were not able to calculate the prevalence of MS in our previous study. In addition, as diagnosis procedure combination hospitals are usually large, the results might have been biased without data from small-scale hospitals and clinics. It is likely that a considerable number of MS patients go to small clinics for their long-term maintenance therapy, so it is

useful to compare differences in patient visits and treatment status between different scales of care settings.

In the present study, we used the database of Japan Medical Data Center Co., Ltd. (JMDC). This is a collection of claims from multiple health insurance societies for Japanese employees. As this database is based on the claims of policyholders rather than on claims collected in hospitals, it contains information about patients visiting all types of care settings, including hospitals, clinics and prescription pharmacies. It also contains population data that enabled us to calculate the prevalence of certain diseases. Using the JMDC database, we carried out the following assessments: (i) we examined the prevalence of MS in Japan, and its recent changes; (ii) we compared patient visit numbers and treatment status between care settings with different numbers of beds, focusing especially on DMT; and (iii) we compared the medical costs of MS with those of other diseases.

Methods

Data sources

The present study used claims data on patients treated in hospitals/clinics from January 2005 to January 2016 obtained from the JMDC database, which contains information from approximately 3 million policyholders covered by multiple Japanese employees’ health insurance societies. As the database stores information about all policyholders, including those who did not visit hospitals or clinics, it enabled us to carry out population-based analyses, such as calculating the prevalence or incidence of specific diseases. In addition, the history of individual patients, including visits and treatments in different care settings (hospitals, clinics and pharmacies) can be traced, provided the patient continued to be covered by the same health insurance. However, the database only contains data for employees and their families, so the majority of individuals were under the age of 65 years and none were older than 75 years, as they were covered by the Advanced Elderly Medical Service System.

Patient identification

MS patients were identified as those diagnosed with code G35, multiple sclerosis, under the 10th Revision of the International Classification of Diseases. The algorithm of patients extraction was the same as our previous study (Table 1).¹² First, we extracted all patients having at least one claim with an MS

Table 1 Methodology for the identification of multiple sclerosis patients

	<i>n</i>	Female (%)	Average age (years)	Coverage period (years)	Observation period (years)
With definitive MS diagnosis	907	62	41.2	4	2.8
With NMO diagnosis	138	67	41.7	3.9	2.2
Without NMO diagnosis	769	61	41.1	4	2.9
① With hospitalization claims with MS diagnosis	290	55	39.2	4.7	3.2
② Other than ① and with outpatient claims with MS diagnosis plus DMT	202	68	42.6	3	2.5
③ Other than ① and ② and MS diagnostic start date before the observation period	220	60	42.4	3.8	3
④ Other than ①, ② and ③ and at least three outpatient claims with MS diagnosis	1	0	46	2.8	2.6
MS patients (①+②+③+④)	713	60	41.2	3.9	3
⑤ Did not meet MS patient criteria	56	64	40.6	4.2	2.5

DMT, disease-modifying therapies; MS, multiple sclerosis; NMO, neuromyelitis optica.

diagnosis during the study period. Second, we excluded any with at least one claim for NMO, coded as Japanese Disease Name Code 3410003. Finally, we included patients who met any of the following criteria:

- (1) at least one hospitalization claim with a definitive MS diagnosis;
- (2) at least one outpatient claim with a definitive MS diagnosis and at least one claim with a DMT prescription;
- (3) at least one outpatient claim with a definitive MS diagnosis and a record of an initial diagnosis of MS from before the study period; or
- (4) at least three outpatient claims with a definitive MS diagnosis.

For a comparison of medical costs, we also used the 10th Revision of the International Classification of Diseases codes to extract data for patients with six diseases similar to MS (i.e. neurodegenerative or autoimmune disorders): myasthenia gravis, Parkinson's disease, amyotrophic lateral sclerosis, ulcerative colitis (UC), Crohn's disease and rheumatoid arthritis (RA).

DMT drugs

DMT drugs were defined as drugs prescribed in Japan for the purpose of preventing a relapse of MS; these include interferon (IFN)- β (1a and 1b), natalizumab, cyclophosphamide hydrate, azathioprine, tacrolimus hydrate, fingolimod, glatiramer acetate and prednisolone. Although some of them (cyclophosphamide hydrate, azathioprine, tacrolimus hydrate and prednisolone) were not approved by the Ministry of Health, Labor and Welfare as DMT drugs, they were used in actual clinical practice. Therefore,

we included these drugs to extract all MS patients from the database and to assess actual treatment status of MS in Japan. As glatiramer acetate was not launched in Japan until November 2015, records with this prescription were not included in the dataset used in the present study. Prednisolone is used not only as a DMT, but also to treat relapse symptoms. At relapse, patients often receive injections of high-dose steroids for acute treatment, followed by oral administrations of steroids including prednisolone, usually for less than a few months. We therefore assumed prednisolones that were prescribed within 3 months of the relapse date as relapse treatments, and excluded them from the analysis. We defined the date of relapse as the date of the first injection of the following relapse treatment drugs at least 30 days after the initial MS diagnosis; prednisolone sodium succinate, dexamethasone phosphate ester sodium or methylprednisolone sodium succinate.

Prevalence

The prevalence of MS in each calendar year was calculated by dividing the total months of insurance coverage of MS patients after their initial definitive MS diagnosis by the total months of insurance coverage across all the policyholders in the year. Obtained values were adjusted according to the age of all policyholders in the dataset after 2011.

Number of patients who mainly visited care settings with different bed numbers

For each MS patient, the main visit to a care setting during a given month was defined by the most

expensive claim (either inpatient or outpatient) during that month. Care settings were categorized by bed numbers, and the number of MS patients whose main visit was found in that category of care settings was counted for each month. The analysis was carried out using data from January 2012 to January 2016.

Prescription of DMT in care settings with different bed numbers

The number of patients who were prescribed DMT was counted in each category of care settings with different bed numbers, and expressed as the percentage of all the patients that visited the care settings of the same category, using data from January 2012 to January 2016. The ratios of patients who were prescribed each DMT drug were analyzed in different periods or years (2012–2013, 2014 and 2015).

Calculation of medical costs

Medical costs from February 2015 to January 2016, including inpatient and outpatient costs and costs of prescription drugs, were analyzed. The cost PPPM was calculated by dividing the total MS medical costs by the total number of months of insurance coverage for all the MS patients. The cost per member per month (PMPM) was calculated by dividing the total MS medical costs by the total number of months of insurance coverage across all policyholders in the database.

Statistical analysis

The statistical analyses were carried out using SAS version 9.2 (SAS Institute, Cary, NC, USA).

Results

Patient profile and prevalence of MS in Japan

A total of 907 patients in the JMDC database had at least one claim with a definitive MS diagnosis between January 2005 and January 2016. Of these, 138 had at least one claim associated with NMO and were therefore excluded from the analysis. From the remaining 769 patients, 56 patients were further excluded, as they did not meet any of the inclusion criteria set out in the Methods section. Finally, 713 patients were identified as MS patients (Table 1).

Table 2 shows the prevalence of MS and the profiles of MS patients in each calendar year from 2011

Table 2 Prevalence of multiple sclerosis and the female-to-male ratios for calendar years 2011–2015

	Calendar year				
	2011	2012	2013	2014	2015
Male	0.012%	0.012%	0.011%	0.012%	0.013%
Female	0.020%	0.021%	0.022%	0.025%	0.026%
Total	0.015%	0.016%	0.016%	0.018%	0.019%
Female/male	1.70	1.72	1.96	2.09	2.03

to 2015. The prevalence of MS increased gradually but continuously from 2011 (0.015%) to 2015 (0.019%). The number of female patients was almost twice that of male patients in each calendar year, and tended to increase during the study period (Table 2).

Status of DMT drug use

In Japan, eight drugs were used as DMT during our study period, including oral fingolimod launched in 2011. We analyzed the transition of the ratio of patients who were prescribed each DMT drug between December 2009 to January 2016 (Fig. 1). The percentage of patients who were prescribed fingolimod rapidly increased after its launch in 2011, whereas the percentage of patients prescribed IFN gradually decreased. In 2015, the share of fingolimod (26.7%) was comparable with those of IFN (28.3%) and prednisolone (31.7%).

Care settings

Figure 2 shows the distribution of the MS patients whose main visit in a certain month was found in care settings of different bed number categories. A total of 46% of the MS patients mainly visited large hospitals with more than 500 beds (110 hospitals). Conversely, 30% of MS patients, the next largest population, visited clinics with fewer than 20 beds (53 clinics).

We then analyzed the percentage of patients prescribed any DMT by care setting category (Fig. 3). The prescription rate of DMT was highest in the larger hospitals, and was positively correlated with the number of beds defining the care setting categories. From 2012 to 2014, fingolimod was the most frequently prescribed DMT in the small clinics with fewer than 100 beds (Fig. 4a,b). The percentage of fingolimod prescriptions increased in 2014 across all care setting categories (Fig. 4a,b). In 2015, the prescription of fingolimod increased in hospitals with more than 100 beds,

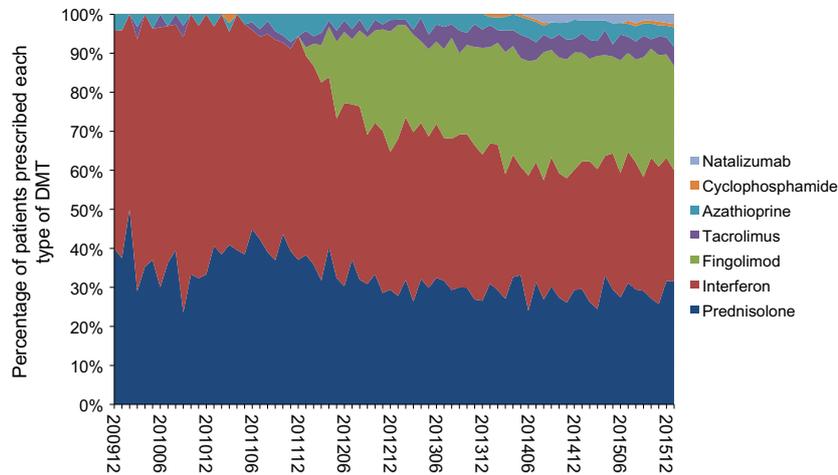


Figure 1 The changing percentage of patients prescribed each disease-modifying therapy (DMT) over the period December 2009 to December 2015. Percentages at each time-point have been scaled according to the total number of patients prescribed DMT at that time (=100%).

but decreased in clinics with fewer than 100 beds (Fig. 4b,c).

Medical costs

We calculated the medical costs for MS and compared them with those for other diseases with similar pathogenic mechanisms and symptoms to MS. The mean medical cost PPPM for MS was estimated to be ¥124 337, which was higher than the costs for Parkinson's disease (¥84 410), myasthenia gravis (¥82 944), UC (¥49 189) and RA (¥53 843; Fig. 5a). However, the mean medical cost PMPM, which represents the economic impact of the disease across all policyholders, was ¥25.2 for MS; this was lower than

the costs for Parkinson's disease (¥123.0), UC (¥114.1) and RA (¥311.6; Fig. 5b).

Discussion

In the present study, we analyzed data from a real-world database, and revealed up-to-date prevalence, treatment status and medical cost information about MS in Japan. Our results showed a recent increase in the prevalence of MS in Japan, as well as in the female-to-male ratio. DMT were more frequently prescribed in larger care settings, and the prescription of fingolimod rapidly increased after its launch in 2011. The medical cost per MS patient was relatively high when compared with the costs for similar diseases, although the medical cost across the total population was comparably low because of the low prevalence of MS in Japan.

The results showed that the prevalence of MS in Japan steadily increased from 0.015% in 2011 to 0.019% in 2015 (Table 2). In Japan, MS is specified as one of the rare, intractable diseases, and almost all the MS patients, especially those who are prescribed DMT drugs, are eligible to receive financial support from the government for medical care. According to the number of recipients of this support, the number of MS patients (including NMO) in Japan was 16 140 in 2011,⁹ which was approximately 0.013% of the total Japanese population. The number of recipients increased to 19 389 (approximately 0.015% of the total population) in 2014, showing an increase in the prevalence of MS in Japan. This increase in the nationwide prevalence of MS was also reported in another study.⁶ Although

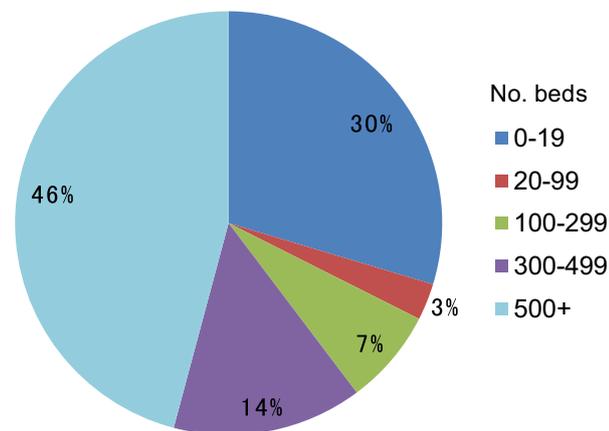


Figure 2 Distribution of multiple sclerosis patients' main visits by care setting category (defined by the number of beds).

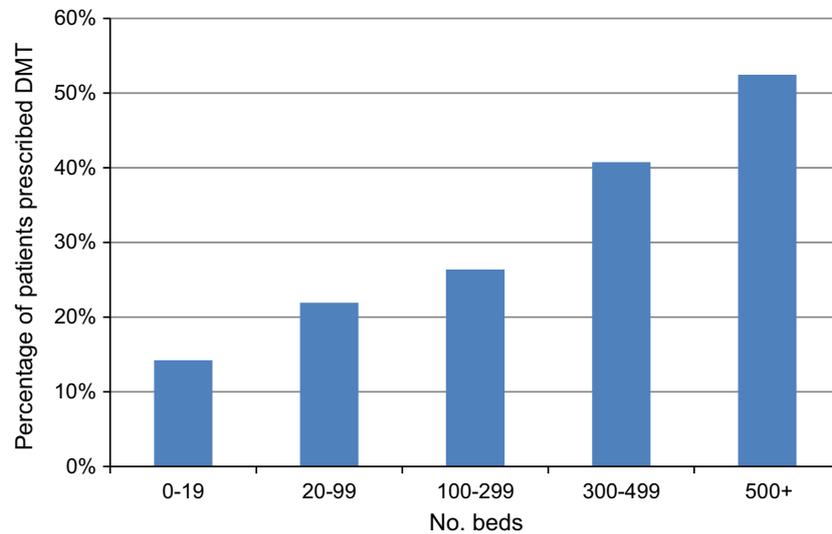


Figure 3 Percentage of disease-modifying therapy (DMT) prescriptions by care setting category (defined by the number of beds).

we extracted just 713 MS patients for analysis, accounting for approximately 3.7% of the total number of MS patients in Japan, our results were consistent with those data, confirming that we were able to carry out a reliable nationwide investigation based on a real-world database. The present results suggest that analysis of real-world data could be applied in the future for obtaining national trends for the prevalence of MS and other rare diseases.

In our data on MS patients, the female-to-male ratio was 1.70 in 2011, increasing consistently to 2.09 in 2014 (Table 2). Other studies have also shown that MS is more common in women, and that the female-to-male ratio was increasing in Japan, as well as in other countries.^{6,8,13–15} However, the absolute value of the prevalence of MS in women in the present study was lower than that (2.9) reported by the previous survey in 2004.⁶ This could be due to a difference in the definition of MS between the studies; as mentioned in the Introduction, the previous studies included NMO within the definition of MS. As the female-to-male ratio for NMO (4.5) is higher than that for MS, this might have led to a higher female ratio in the previous study.

The increased prevalence of MS and the increased female-to-male ratio might be explained by environmental changes in the exposure to risk factors, such as ultraviolet radiation¹⁶ or reduced microbial burden during childhood.¹⁷ Conversely, an increase in early diagnosis enabled by magnetic resonance imaging, or the longer survival with MS achieved with DMT therapy, could partially explain the increased diagnosed prevalence.¹⁸

As the JMDC database is based on the claims data of policyholders rather than the claims data obtained from individual hospitals, it was possible for us to compare patient visits and treatment status between care settings of different scales. The greatest proportion of MS patients had their main visits at large hospitals with more than 500 beds (Fig. 2). In contrast, the second-largest population of patients have their main visits at small clinics with fewer than 20 beds (Fig. 2). MS is one of the rare diseases that require detailed examination for a definitive diagnosis, including magnetic resonance imaging and cerebrospinal fluid examination. The prescription of DMT also requires careful evaluation and monitoring at the beginning, sometimes including hospitalization. During the early stage of MS, therefore, most patients are likely to visit large hospitals. However, because MS requires long-term treatment, a significant number of patients might change their care setting to a small clinic more convenient for maintenance treatments. It is likely that patients visit small clinics more frequently than large hospitals, which might have led to the apparent increase in the percentage of patients visiting small clinics.

The rate of DMT prescriptions was positively correlated with the care setting category bed numbers (Fig. 3). As mentioned earlier, administering a DMT needs careful monitoring, and some DMT drugs are known to cause severe adverse effects.^{19–21} DMT might therefore be prescribed more frequently in larger hospitals. The prescription of fingolimod rapidly increased from 2011, after its launch in Japan, and consistently maintained its share of approximately

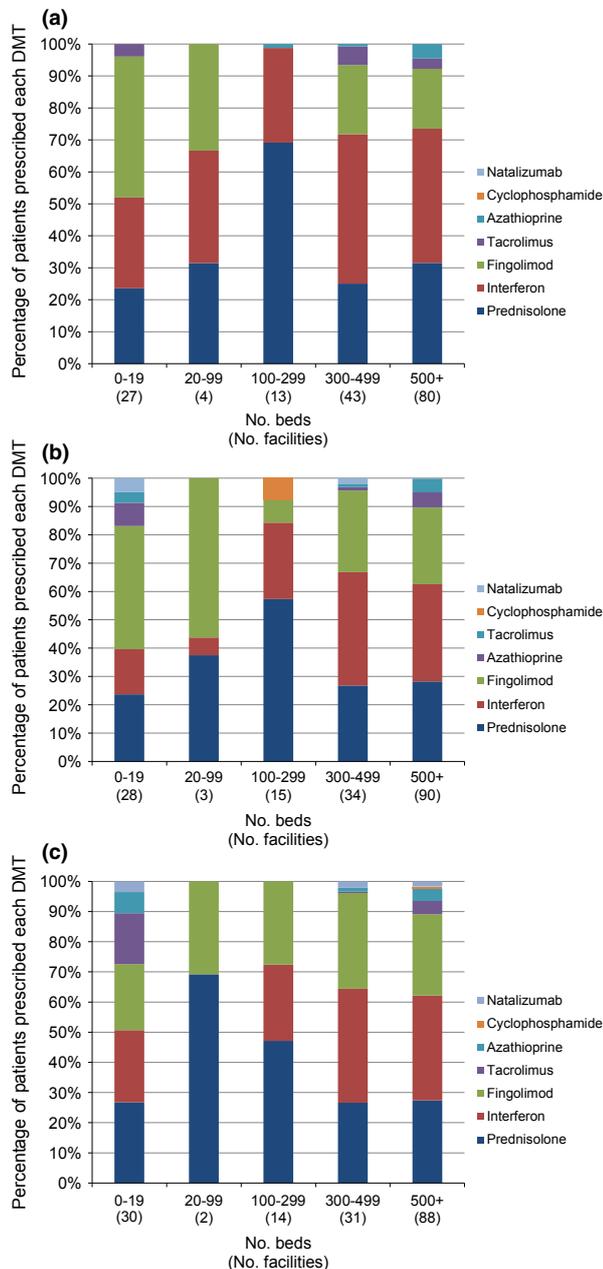


Figure 4 Percentage of patients who were prescribed each type of disease-modifying therapy (DMT) by care setting category (defined by the number of beds) during (a) 2012–2013, (b) 2014 and (c) 2015 (all patients who were prescribed DMT during the period =100%).

one-third of total DMT prescriptions (Fig. 1). Fingolimod is the first oral DMT drug in Japan. Although its long-term efficacy and safety in clinical practice have not been completely established in Japan, fingolimod has been widely used in many other countries. Because of its convenience for patients, small clinics might prefer to prescribe fingolimod over other DMT that require injection (Fig. 4).

In our data, the proportion of fingolimod prescribed in hospitals with 100–299 beds was lower than for any other care setting category between 2012 and 2014 (Fig. 4a,b). In addition, the ratio of cyclophosphamide prescription was considerably higher in this category of care setting in 2014 (Fig. 4b). A possible reason for this could be that the number of hospitals in this category was relatively small, and therefore might have been disproportionately affected by the data of particular hospitals with specific treatment policies. Immunosuppressants, including cyclophosphamide, are usually used for patients who failed with initial DMT treatment. Therefore, it might also be possible that patients who were unsuccessful in their initial treatment in large hospitals have visited medium-sized hospitals to seek alternative therapies.

The mean medical cost PPM calculated in the present study (¥124 337) was approximately 32% higher than that in our previous study (¥93 542).¹¹ We previously reported that the medical costs for MS were significantly higher for patients aged <50 years, because of the greater proportion of the cost attributable to DMT.¹¹ The mean age of MS patients extracted from the JMDC database in the present study was approximately 41 years, which is younger than that in our previous study using Medical Data Vision's database (50.4 years) due to the difference in parent population between these databases. As the JMDC database only contains claims data of employees and their families, the proportion of data for patients aged >65 years is small (2.7%). This difference in the characteristics of the two databases might explain the higher medical cost for MS in the present study.

The mean medical cost PPM (the monthly cost for a patient) for MS was ¥124 337, which was higher than the median value (¥82 944) of the mean medical costs PPM of seven similar diseases (Fig. 5a). It was almost 2.3-fold higher than the cost for RA (¥53 843), one of the most common autoimmune diseases in Japan. In contrast, the medical cost PPM (the monthly cost divided across all policyholders) for MS (¥25.2) was lower than the median value (¥88.1) of the mean medical costs of similar diseases (Fig. 5b), and was approximately one-twelfth of that of RA (¥311.6). These results show that although the cost for MS treatment was relatively expensive, its overall impact on total medical cost in Japan was relatively limited because of the low prevalence of MS. However, as the prevalence of MS is increasing and the costs of DMT are expected to rise, it is important to keep track of the latest trends in the medical costs for MS in Japan.

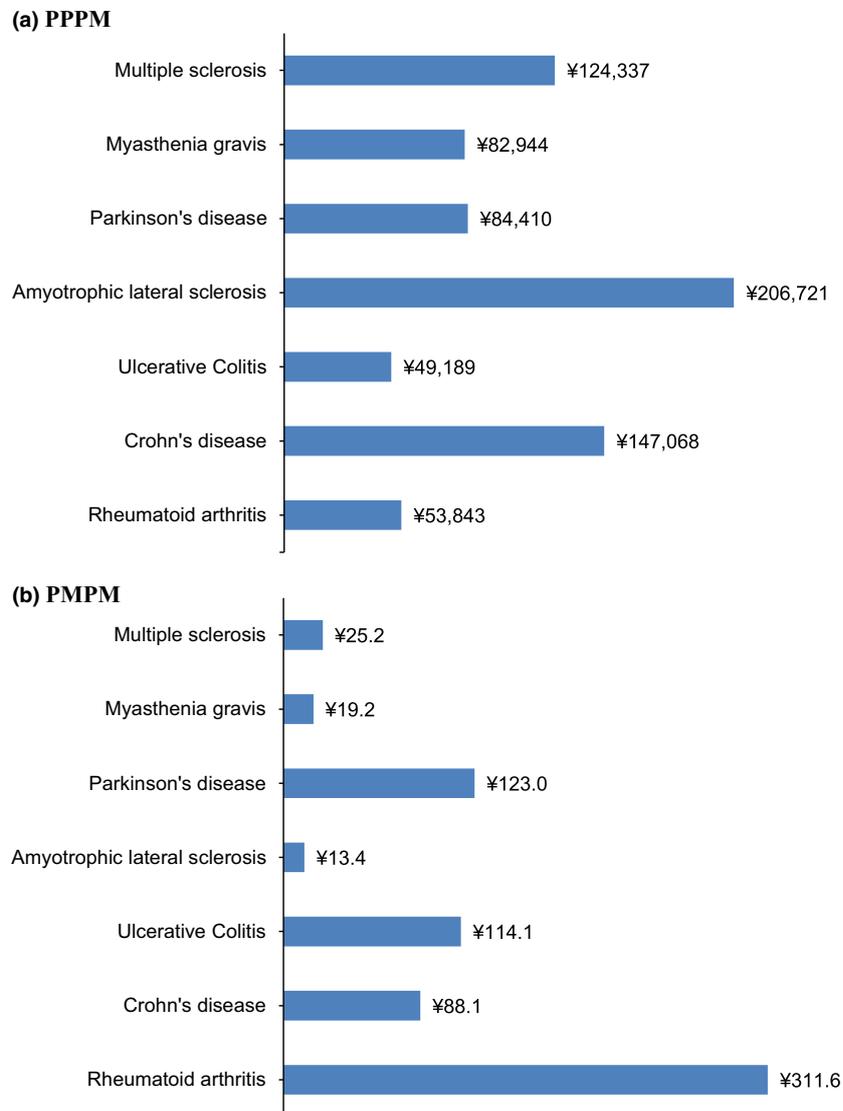


Figure 5 Comparison of the medical costs, (a) per patient per month (PPPM) and (b) per member per month (PMPM), of multiple sclerosis with those of similar immune or neurodegenerative diseases.

The present study had several limitations. The JMDC database comprises health insurance claims for company employees and their families. In Japan, patients aged >75 years are covered by the Advanced Elderly Medical Service System, so the patients' ages in the present study were limited to those aged <75 years, with most aged <65 years. In addition, an individual patient's history could not be traced after discharge or retirement from the company. Although JMDC collects data from all over Japan, we cannot exclude the possibility that there might have been regional bias in the data.

In conclusion, we analyzed claims data from JMDC, and provided nationwide, up-to-date data on

the prevalence, treatment status and medical costs of MS in Japan. As the prevalence of MS is continually increasing in Japan and the cost for DMT accounts for the greatest part of the medical costs of MS, it is interesting to have obtained data about the trends in DMT prescription in recent years. These results could provide important information that helps clinicians and policymakers to offer better treatments for MS patients.

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Disclosure of ethical statements

No human participant was involved in this study.

Conflict of interest

Mieko Ogino has received funding for travel from Takeda Pharmaceutical Company Limited. Izumi Kawachi has received funding for research, travel and/or speaker honoraria from Novartis Pharma, Biogen, Bayer Yakuhin Limited, Mitsubishi Tanabe Pharma, Takeda Pharmaceutical Company Limited, Japan Blood Products Organization, and Astellas Pharma, and is a scientific advisory board member for Biogen and Takeda Pharmaceutical Company Limited. Shuichi Okamoto, Hiroyuki Ohta, Mariko Sakamoto, Manami Yoshida and Shinzo Hiroi are employees of Takeda Pharmaceutical Company Limited. Yusuke Nakamura and Kosuke Iwasaki are employees of Milliman. Financial support for writing and editorial assistance was provided by Takeda Pharmaceutical Company Limited.

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