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Original article

Insights from the trends of omalizumab and mepolizumab utilization in patients with asthma: A population-based cohort study using the National Database in Japan

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ABSTRACT

Background: Biologics are increasingly being used in patients with severe uncontrolled asthma. However, the trends in their use for treating severe asthma in Japan remain unclear.
Methods: The number of patients with asthma prescribed omalizumab or mepolizumab between April 2017 and March 2018 was estimated according to sex, age, and geographical region using data from the National Database of Health Insurance Claims and Specific Health Checkups of Japan.
Results: Overall, 5,014, 3,449 and 7,977 patients were prescribed omalizumab, mepolizumab, or either combination, respectively. The total number of patients prescribed biologics displayed a bimodal distribution with peaks in their early teens and seventies. Biologics were most commonly used by male and female patients in their seventies. Prescription was 1.24 times higher in males than in females up to the teenage years, whereas it was 1.95 times higher in females than in males from their twenties onwards. Omalizumab was prescribed 1.45 times more frequently than mepolizumab, especially in pediatric patients, and was prescribed 1.96 times more often to female patients than to male patients. Regional differences were observed in the proportion of patients prescribed biologics. Correlation analysis suggested a weak relationship ($r = 0.3226$, $p = 0.0270$) between the proportion of patients prescribed biologics and board-certified allergists according to the geographic region.
Conclusions: In Japan, biologics are prescribed more often to older patients with severe asthma compared to those in other countries. Thus, eliminating the regional disparities in asthma treatment by specialists is necessary to provide appropriate medical care to patients with severe asthma.

Abbreviations: NDB, the National Database of Health Insurance Claims and Specific Health Checkups of Japan; ICD-10, International Classification of Diseases-10; MHLW, the Ministry of Health, Labour and Welfare.

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1. Introduction

Asthma is a heterogeneous disease that affects approximately 262 million people and causes 455,000 deaths worldwide [1,2]. Inhaled corticosteroids are effective at improving asthma control and preventing its exacerbation in pediatric and adult patients; they have thus contributed to a reduction in mortality [3–5]. However, approximately 5–10 % of patients have severe uncontrolled asthma despite adherence to the standard treatment with high-dose inhaled corticosteroids and additional controllers [6–8]. Patients with severe uncontrolled asthma show increased hospitalization, exacerbation requiring treatment with systemic corticosteroids, and poor quality of life [9,10].

A recent understanding of the variable clinical phenotypes and distinct underlying pathophysiological endotypes has led to the development of new treatment strategies for patients with severe asthma: biologics [11–13]. The currently approved biologic agents target key modulators of inflammation, such as IgE, IL-5, IL-4/IL-13, and thymic stromal lymphopoietin [7,13]. Omalizumab (Xolair®), a humanized anti-Ig-E monoclonal antibody (mAb), was the first biologic approved for treating severe adult asthma and has been available in Japan since 2009. Anti-IL-5 mAb mepolizumab (Nucala®) was the second biologic approved in Japan in 2016, and targets eosinophils by preventing IL-5 binding to its receptor and subsequent eosinophil recruitment and activation. For children, omalizumab and mepolizumab (twelve years old and over) have been available in Japan since 2013 and 2016. Owing to ample evidence regarding the benefits of biologics and various biological options, a recent increase has been reported in the use of biologics [14–16]. However, little is known about the trends in their utilization for severe asthma in Japan.

Strategic Outlook toward 2030: Japan's Research for Allergy and Immunology (Strategy 2030) is the national research strategy based on Japan's Basic Act on Allergic Diseases and Measures, the first of its kind worldwide [17]. As part of this *Strategy 2030*, the Task Force conducted and reported an epidemiological study on allergic diseases using The National Database of Health Insurance Claims and Specific Health Checkups of Japan (NDB) [18]. The NDB is a comprehensive database of health insurance claims covered by the Japanese National Health Insurance System and is considered representative of almost all health claims databases containing medical care datasets generated from insured inpatient and outpatient visits. No previous studies have examined the trends in biologic utilization for severe asthma at all ages using a real-world database covering almost all of Japan. Japan has been categorized as a super-aged society. In 2020, 28.8 % of the total population was aged 65 or older and this proportion is expected to exceed 35 % in 2040 [19]. The asthma mortality rates among the 5–34 years age group in Japan were reported to be considerably lower than the average rate of asthma deaths in 46 countries [20]. However, the proportion of people aged 65 and older with asthma deaths exceeded 90 % in 2017 [21]. With an increasing aging population worldwide, preventing asthma deaths in the elderly is considered an important issue in Japan and other countries. The NDB analysis will help clarify the epidemiology and characteristics of severe asthma in all age groups, including the elderly, and the medical issues to be addressed as barriers to the use of biologics. Therefore, we aim to identify the trends in biologic utilization for asthma from April 2017 to March 2018 using the NDB and elucidate the regional disparities in their use and the barriers to biologic treatment.

2. Patients and methods

2.1. Data and study design

We conducted a population-based retrospective cohort study using an NDB dataset, as previously reported [18]. The study cohort comprised individuals enrolled in the NDB, as previously reported. Thus, the NDB includes almost all patients regardless of the type of insurance because Japan has a universal health coverage system.

The NDB database provides information on each patient's personal identifier (ID variable), dates of prescriptions and medical visits, age group, sex, region where the procedures were carried out, a description of these procedures, the World Health Organization International Classification of Diseases-10 (ICD-10) diagnosis codes, and information on the medical care received. The NDB also contains information on the prescribed drugs, including the prescription amount, brand name, generic name, dosage, and number of days a given medication was prescribed. The NDB includes anonymized patient personal identification variables and allows the longitudinal follow-up of each patient using a patient matching technique in the NDB database [22].

This study was approved by the ethics committee of Nara Medical University (project approval number, 2831) and was conducted in accordance with the tenets of the Declaration of Helsinki and its later amendments. The claims database used in this study was collected by Labour Research Grant from the Ministry of Health, Labour and Welfare (MHLW) of Japan, which was based on law without obtaining informed consent.

2.2. Data extraction

We were granted permission to access the NDB as members of a research group funded by a Health Science and Labour Research Grant from the MHLW of Japan. We extracted data from the original NDB database for all patients diagnosed with asthma (ICD-10 codes J45, J46, and O995) and prescribed omalizumab (Xolair® 75 mg/Xolair ® 150 mg) or mepolizumab (Nucala® 100 mg) at least once based on the data collected between April 2017 and March 2018. Facilities where biologics were prescribed were classified into two categories: clinics or hospitals. The NDB counted the number of patients prescribed biologics according to the address of the facility, not the patient's residence.

During this period, omalizumab and mepolizumab were available to patients with severe asthma in Japan. Omalizumab was also administered to patients aged 12 years and older with chronic urticaria. Patients who were prescribed omalizumab for chronic urticaria could not be distinguished based on the data extracted in this study if they were diagnosed with both asthma and chronic urticaria. All diagnoses and drug codes are listed in Supplementary Table 1. The extracted data were expressed as counts per 100,000 population or 1,000 asthma patients, as well as by the 10-year age group, sex, and region, using the population estimate of Japan in 2017 b y the Ministry of Internal Affairs and Communications (https://www.stat.go.jp/english/index.html) and the estimated number of asthma patients or asthma deaths in 2017 b y the MHLW (https://www.e-stat.go.jp/en/). The number of available allergists was obtained from the Japanese Society of Allergology website (https://www.jsaweb.jp/modules/ninteilist_general/).

2.3. Statistical analysis

Correlations were examined using Spearman's correlation. All statistical analyses were conducted using JMP Pro 16.0 (JMP, Marlow, Buckinghamshire, UK). Probability values < 0.05 were considered significant, and all tests were two-tailed.

3. Results

3.1. Number of patients prescribed biologics by sex and age group

The number of patients with asthma who were prescribed biologics (omalizumab or mepolizumab) was 7,977; biologics were prescribed to 1.83 times as many female patients than male patients from April 2017 to March 2018. Fig. 1A shows the bimodal distribution of the total number of patients prescribed biologics (omalizumab or mepolizumab), in which peaks were observed in the early teens and seventies. The total number of patients prescribed biologics was 1.24 times higher in males

than in females up to their teenage years, whereas it was 1.95 times higher in females than in males from their twenties onwards. Biologics were most commonly used by male and female patients in their seventies. A systematic review of 40 real-world studies published in 2008–2018 (n = 9,240) showed that the average age of patients receiving omalizumab was 52.3 years [23]. Therefore, in Japan, biologics are prescribed more often to older patients with severe asthma compared to those in other countries. The number of patients prescribed biologics by sex and age group showed similar trends to the number of patients prescribed per 100,000 population by sex and age group (Fig. 1B). Next, we analyzed the proportion of patients prescribed per 1,000 asthmatic patients using the estimated number of patients with asthma in 2017 b y the MHLW (Fig. 1C). Unlike Fig. 1A and B, female patients were more likely to be prescribed than male patients, except for those in their sixties, and the proportion of patients prescribed per asthmatic patient dropped in their sixties.

From April 2017 to March 2018, the number of patients with asthma prescribed omalizumab and mepolizumab was 5,014 and 3,449, respectively. Omalizumab and mepolizumab were prescribed 1.96 and 1.66 times more to female patients than to male patients, respectively. Both omalizumab and mepolizumab were prescribed more frequently to males than to females up to their teenage years, with the trend reversing after their twenties (Table 1 and Fig. 2). The highest age of patients prescribed omalizumab was 75–79 years, while for mepolizumab, it was 70–74 years. Omalizumab was used 1.45 times more frequently than mepolizumab, especially in pediatric patients, and was prescribed 1.96 times more often to female patients than to male patients.

3.2. Categories of the facilities where biologics were prescribed

The categories of facilities where biologics were prescribed were classified as clinics or hospitals. If the same patient received prescriptions for biological agents across hospitals and clinics between April 2017 and March 2018, they were counted separately for each institution. In that case, 5,081, 3,471 and 8,076 cases were prescribed omalizumab, mepolizumab, or either combination, respectively, as shown in Fig. 3. Ninety-two cases could not be classified because of unknown details. Although omalizumab was available in Japan seven years before mepolizumab, the proportion of the categories of facilities where each biologic was prescribed was almost equal for each, with 80 % of prescriptions being given in hospitals.

3.3. Number of patients prescribed biologics by geographic region

The number of patients prescribed omalizumab, mepolizumab, or their total for all ages per 100,000 people, according to geographic

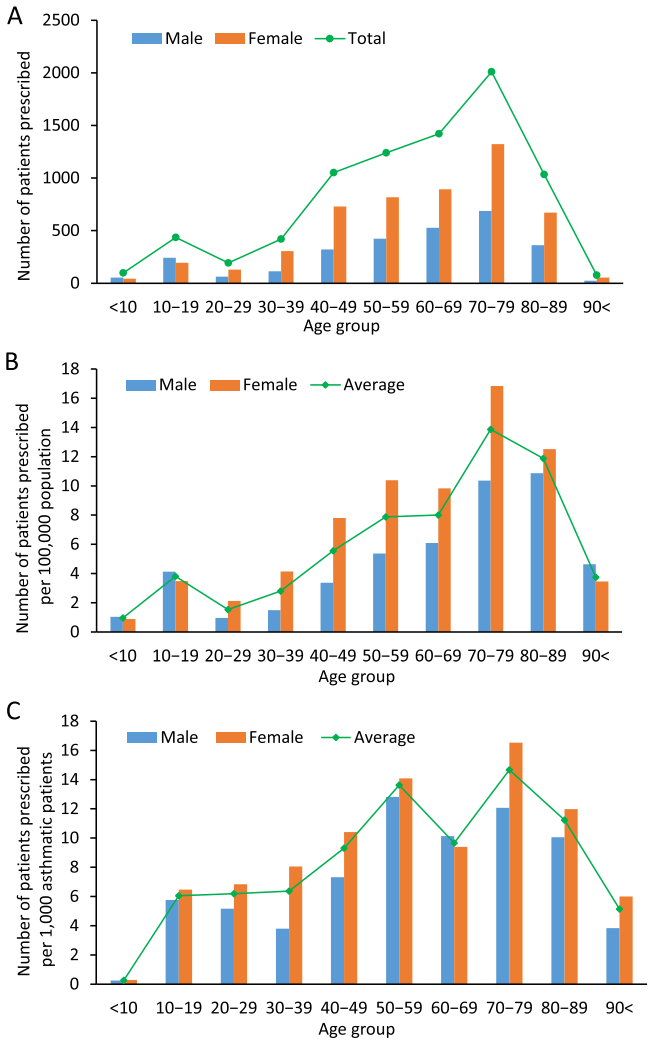

Fig. 1. The number of patients prescribed omalizumab or mepolizumab by sex and age group. The numbers of patients (A), patients per 100,000 people (B), and patients per 1,000 patients with asthma (C) are shown.

Table 1
The number of patients prescribed biologics by sex and age group.

Age	Omalizumab			Mepolizumab		
Years	Male	Female	Ratio	Male	Female	Ratio
<10	53 (1.02)	44 (0.89)	1.20 (1.15)	0 (0.00)	0 (0.00)	–
10–14	124 (4.49)	105 (3.96)	1.18 (1.13)	30 (1.08)	19 (0.72)	1.58 (1.50)
15–19	79 (2.57)	64 (2.19)	1.23 (1.17)	25 (0.81)	16 (0.55)	1.56 (1.47)
20–24	15 (0.47)	41 (1.36)	0.37 (0.35)	NR	NR	NR
25–29	18 (0.56)	68 (2.22)	0.26 (0.25)	21 (0.65)	21 (0.68)	1.00 (0.96)
30–34	31 (0.86)	94 (2.69)	0.33 (0.32)	20 (0.55)	52 (1.49)	0.38 (0.37)
35–39	43 (1.08)	135 (3.47)	0.32 (0.31)	30 (0.75)	44 (1.13)	0.68 (0.66)
40–44	78 (1.63)	247 (5.30)	0.32 (0.31)	52 (1.09)	104 (2.23)	0.50 (0.49)
45–49	130 (2.72)	268 (5.73)	0.49 (0.47)	88 (1.84)	146 (3.12)	0.60 (0.59)
50–54	99 (2.42)	270 (6.65)	0.37 (0.36)	114 (2.78)	172 (4.24)	0.66 (0.66)
55–59	120 (3.17)	237 (6.23)	0.51 (0.51)	117 (3.09)	194 (5.10)	0.60 (0.61)
60–64	134 (3.48)	214 (5.41)	0.63 (0.64)	116 (3.02)	197 (4.98)	0.59 (0.61)
65–69	154 (3.21)	297 (5.80)	0.52 (0.55)	160 (3.33)	252 (4.92)	0.63 (0.68)
70–74	184 (5.07)	387 (9.39)	0.48 (0.54)	175 (4.82)	318 (7.72)	0.55 (0.62)
75–79	208 (6.91)	392 (10.51)	0.53 (0.66)	173 (5.75)	312 (8.36)	0.55 (0.69)
80–84	155 (7.19)	296 (9.44)	0.52 (0.76)	122 (5.66)	218 (6.95)	0.56 (0.81)
85–89	53 (4.52)	127 (5.72)	0.42 (0.79)	47 (4.01)	70 (3.15)	0.67 (1.27)
90<	19 (3.83)	40 (2.57)	0.48 (1.49)	NR	NR	NR

NR: not reported. The values and the values in parentheses indicate the number of patients prescribed biologics and the number of patients prescribed biologics per 100,000 population by sex and age group, respectively. The number of patients prescribed mepolizumab for males and females aged 20–24 and males aged 90< is not reported owing to the small sample size. The number of patients prescribed mepolizumab for females aged 90< is not reported to prevent back-calculation the number of males.

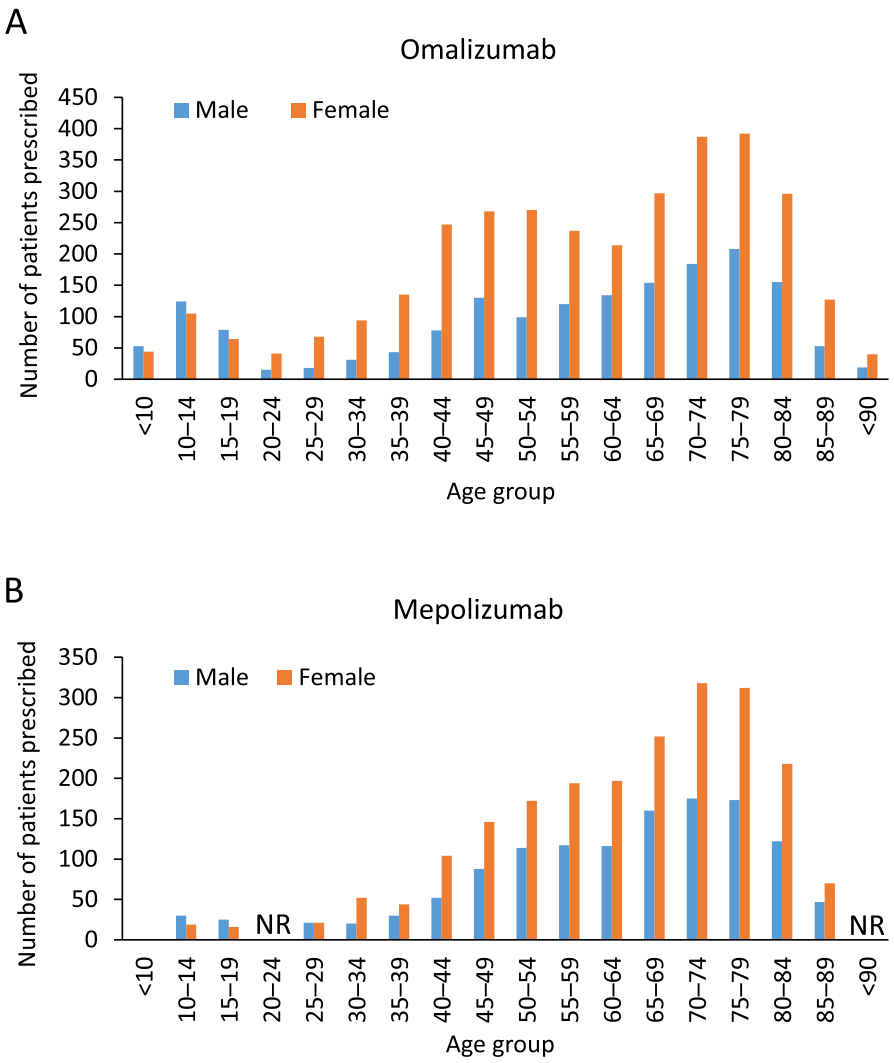

Fig. 2. The number of patients prescribed omalizumab alone (A) or mepolizumab alone (B) by sex and age group. NR: not reported. The number of patients prescribed mepolizumab for males and females aged 20–24 and males aged 90< is not reported owing to the small sample size. The number of patients prescribed mepolizumab for females aged 90< is not reported to prevent back-calculation the number of males.

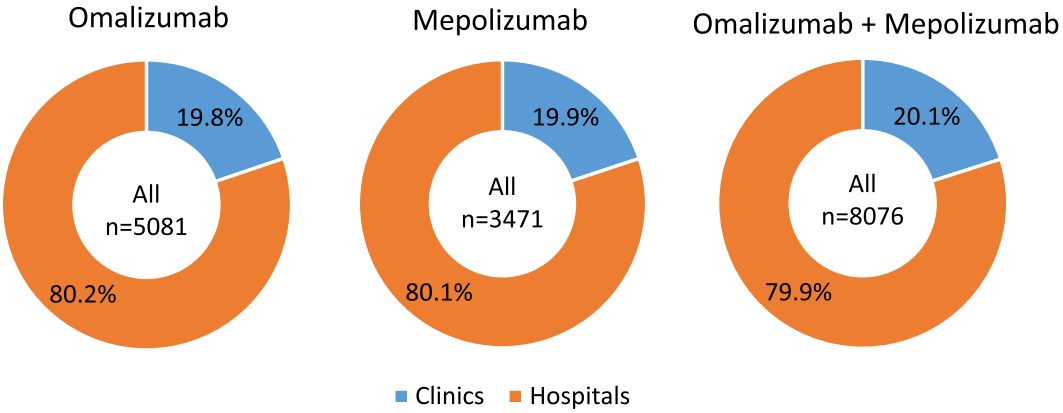

Fig. 3. Categories of the facilities where biologics were prescribed in all cases.

region, is shown in Table 2 and Fig. 4. The number of patients prescribed biologics (omalizumab or mepolizumab) was higher in Tokyo (2,159), Kanagawa (714), Osaka (459), and Kyoto (383). The number of patients prescribed biologics per 100,000 people by geographic region was higher in Tokyo (15.73), Kyoto (14.74), Fukui (12.32), Kanagawa (7.80), and Ibaraki (7.05). The incidence of omalizumab use was higher in Fukui (9.88), Kyoto (9.27), Tokyo (9.17), Ibaraki (5.36), and Kanagawa (5.35), while that of mepolizumab use was higher in Tokyo (7.51), Kyoto (6.54), Fukui (3.85), Hiroshima (3.57), and Gunma (3.42). Omalizumab was more commonly used than mepolizumab except in Tochigi, Gunma, Toyama, Wakayama, Tottori, Shimane, Hiroshima, Kochi, and Kagoshima. Correlation analysis suggested a weak relationship between the number of patients prescribed mepolizumab alone ($r = 0.4106$, $p = 0.0041$; Fig. 5B) and omalizumab or mepolizumab ($r = 0.3226$, $p = 0.0270$; Fig. 5C) per 100,000 people and the number of board-certified allergists (internal medicine and pediatrics) per 100,000 people, according to geographic region, but not omalizumab alone ($r = 0.1941$, $p = 0.1910$; Fig. 5A). No correlation was found between the number of patients who were prescribed biologics (omalizumab or mepolizumab) per 100,000 people and the number of asthma deaths per 100,000 people according to the geographic region (Supplementary Fig. 1.)

4. Discussion

We conducted the first epidemiological study of biological utilization for asthma using the NDB, a nationwide claims database comprising almost all the medical database information in Japan. First, we investigated the trends of biologics utilization in 2017, the first year in which omalizumab and mepolizumab became available. We are currently investigating the changes in the number of patients with asthma using biologics over time since 2015.

In 2017, omalizumab was prescribed more to patients with severe asthma than mepolizumab in Japan. Similar trends were reported in other countries. According to the International Severe Asthma Registry and the US CHRONICLE study, of the 2266 patients with asthma receiving biologics in 2017, omalizumab and mepolizumab was used in 60.3 % and 35.9 %, respectively. However, mepolizumab (53.3 %) was used more than omalizumab (39.4 %) among the 1016 patients who started using a biologic for the first time in 2017 [24]. Akenroye et al. reported the trends of biologic use in the United States using the IQVIA National Disease and Therapeutic Index, a nationally representative, all-payer audit of ambulatory care in the United States [14]. Ambulatory asthma visits treated with omalizumab were higher than those with mepolizumab in 2017 in the United States, and this trend continued into 2019, with omalizumab accounting for 36.6 % of all visits treated with biologics and mepolizumab accounting for 21.4 %.

In this study, the number of patients prescribed omalizumab or mepolizumab by sex and age group showed a similar trend to the number of patients with asthma in Japan, with higher prescription in males than in females up to their teenage years and higher prescription in females than in males from their twenties onwards [25]. However, the proportion of patients prescribed biologics per 1000 asthmatic patients was higher among adolescent females, suggesting that adolescent females may have more severe asthma than adolescent males (Fig. 1C). In fact, in previous observational studies, the incidence ratio for asthma hospitalization for females *vs*. males increased in adolescents and adults, and the incidence rate of rehospitalization showed little sex difference between the ages of 1 and 9 years, but was markedly higher in females than in males aged 10–19 years [26–28]. In addition, the number of patients prescribed for biologics was decreased in their twenties compared to those in their teens (Figs. 1 and 2). This may indicate that the Japanese subsidies for children's medical care often cover children under 20 years of age and that the problem of transitional medical care arises for those who are 20 years of age or older.

Akenroye et al. also reported that patients with asthma aged 45–64 years were treated with biologics more often than patients aged 65 years and over in 2019 in the United States [14]. A systematic review of 40 real-world studies published in 2008–2018 ($n = 9240$) showed that the average age of patients receiving omalizumab was 52.3 years [23]. However, the number of patients prescribed biologics peaked in their seventies in our study (Fig. 1A and B). Elderly patients with asthma account for a high proportion of asthma-related deaths in Japan, with those aged 65 years or older accounting for an increasing proportion of 91.6 % in 2017 [21]. Severe asthma in the elderly is a critical issue to be solved for preventing asthma-related deaths. However, despite the

Table 2
The number of patients prescribed biologics by geographic region.

Geographic region	Omalizumab	Mepolizumab	Geographic region	Omalizumab	Mepolizumab
Total	5,014 (3.96)	3,449 (2.72)	24. Mie	53 (2.94)	31 (1.72)
1. Hokkaido	197 (3.70)	108 (2.03)	25. Shiga	44 (3.11)	32 (2.26)
2. Aomori	53 (4.15)	23 (1.80)	26. Kyoto	241 (9.27)	170 (6.54)
3. Iwate	36 (2.87)	36 (2.87)	27. Osaka	282 (3.20)	202 (2.29)
4. Miyagi	94 (4.05)	32 (1.38)	28. Hyogo	164 (2.98)	106 (1.93)
5. Akita	53 (5.32)	15 (1.51)	29. Nara	45 (3.34)	21 (1.56)
6. Yamagata	21 (1.91)	13 (1.18)	30. Wakayama	16 (1.69)	19 (2.01)
7. Fukushima	49 (2.60)	26 (1.38)	31. Tottori	15 (2.65)	17 (3.01)
8. Ibaraki	155 (5.36)	59 (2.04)	32. Shimane	18 (2.63)	19 (2.77)
9. Tochigi	50 (2.55)	53 (2.71)	33. Okayama	72 (3.78)	58 (3.04)
10. Gunma	58 (2.96)	67 (3.42)	34. Hiroshima	89 (3.15)	101 (3.57)
11. Saitama	148 (2.02)	116 (1.59)	35. Yamaguchi	71 (5.13)	33 (2.39)
12. Chiba	182 (2.91)	121 (1.94)	36. Tokushima	NR	NR
13. Tokyo	1,258 (9.17)	1,031 (7.51)	37. Kagawa	42 (4.34)	24 (2.48)
14. Kanagawa	490 (5.35)	271 (2.96)	38. Ehime	44 (3.23)	29 (2.13)
15. Niigata	67 (2.96)	44 (1.94)	39. Kochi	13 (1.82)	18 (2.52)
16. Toyama	21 (1.99)	31 (2.94)	40. Fukuoka	118 (2.31)	95 (1.86)
17. Ishikawa	29 (2.53)	29 (2.53)	41. Saga	NR	NR
18. Fukui	77 (9.88)	30 (3.85)	42. Nagasaki	29 (2.14)	10 (0.74)
19. Yamanashi	17 (2.07)	14 (1.70)	43. Kumamoto	68 (3.85)	23 (1.30)
20. Nagano	45 (2.17)	36 (1.73)	44. Oita	22 (1.91)	12 (1.04)
21. Gifu	38 (1.89)	26 (1.29)	45. Miyazaki	24 (2.20)	22 (2.02)
22. Shizuoka	156 (4.24)	65 (1.77)	46. Kagoshima	29 (1.78)	32 (1.97)
23. Aichi	204 (2.71)	117 (1.55)	47. Okinawa	21 (1.46)	15 (1.04)

NR: not reported. The values and the values in parentheses indicate the number of patients prescribed biologics and the number of patients prescribed biologics per 100,000 population by geographic region, respectively. The number of patients prescribed mepolizumab in Tokushima and Saga is not reported owing to the small sample size. The number of patients prescribed omalizumab in Tokushima and Saga is not reported to prevent back-calculation the number of mepolizumab.

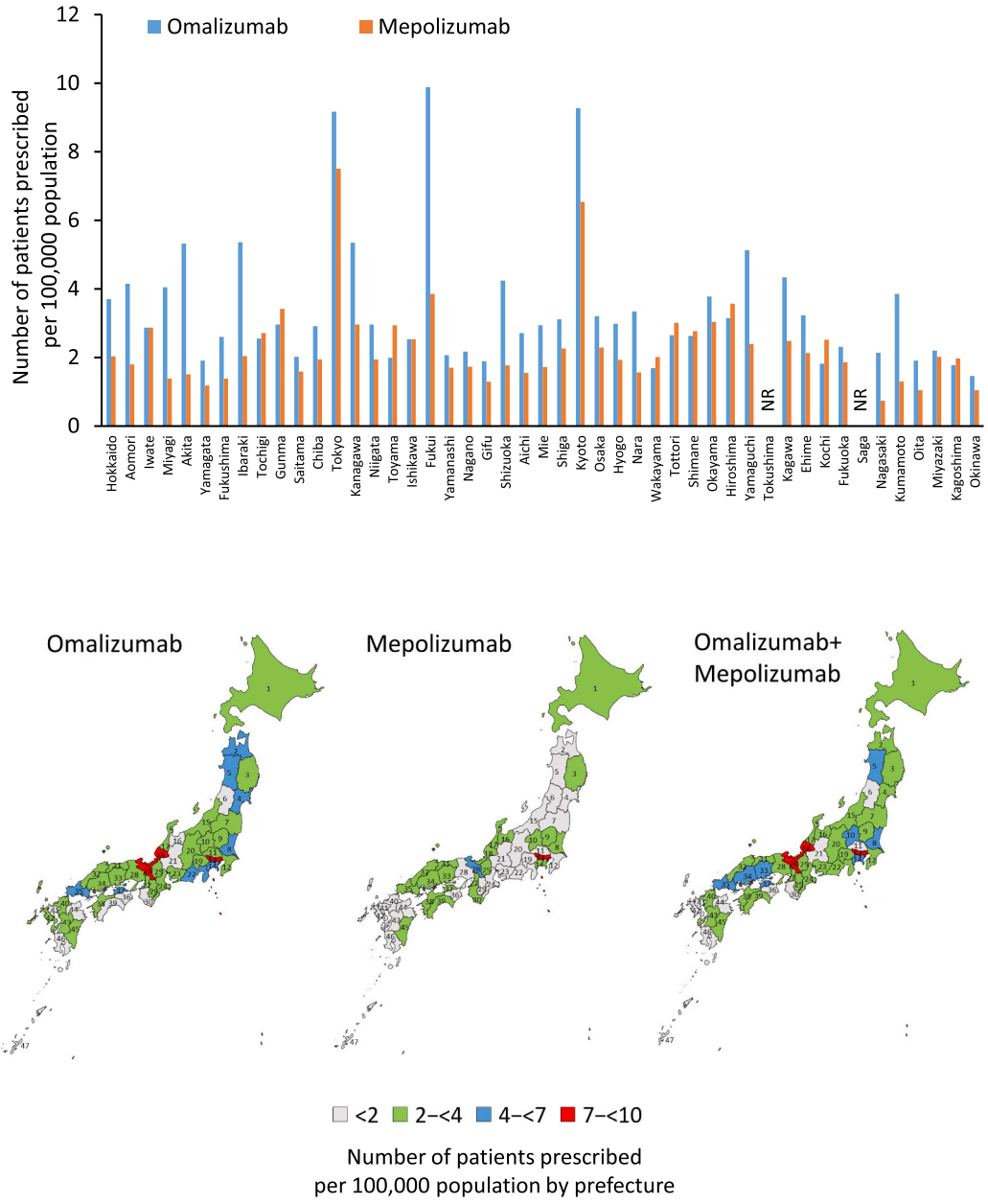

Fig. 4. The number of patients prescribed biologics per 100,000 people by geographic region in all cases.

highest estimated number of asthmatic patients in their sixties in 2017 (Supplementary Fig. 2), the proportion of asthma patients prescribed biologics plummeted in their sixties, especially among females [29]. Financial barriers may be one of the reasons for the fall in their sixties due to retirement from work or higher co-payments of medical expenses in the sixties than in the seventies in Japan (Supplementary Fig. 3). In this study, we also revealed regional disparities in the use of biologics. In 2017, the asthma mortality rate per 100,000 people (mean:1.4) was higher in Kagoshima (3.3), Okinawa (2.7), and Miyazaki (2.6). The number of patients prescribed biologics per 100,000 people (mean:6.30) was <3.60, and the number of board-certified allergists (internal medicine and pediatrics) per 100,000 people (mean:2.4) was <1.0 in 2017 in these three prefectures. From a national perspective, although further studies are needed, correlation analysis suggested a weak relationship between the proportion of patients prescribed biologics and board-certified allergists according to the geographic region (Fig. 5C). These data suggest that regional disparities in the use of biologics depend on the number of available physicians with expertise in asthma treatment. Considering that the number of patients prescribed biologics and asthma deaths are more common in the elderly, eliminating the maldistribution of specialists and removing regional disparities in the treatment of severe asthma may be essential for achieving the "zero death from asthma strategy." No correlation was found between biological prescriptions and asthma mortality rate according to geographic region in the 2017 single-year study (Supplementary Fig. 1). However, this correlation needs to be examined because the number of biologics available for severe asthma has increased in recent years, and the number of prescriptions is also growing compared to that in 2017.

This study had several limitations. Omalizumab was used for patients with asthma aged 12 years or in adult patients with chronic urticaria in 2017 in Japan. However, we did not determine whether omalizumab was prescribed for asthma or chronic urticaria in patients with both asthma and chronic urticaria. Therefore, the possibility of overestimation of the number of patients prescribed omalizumab for asthma

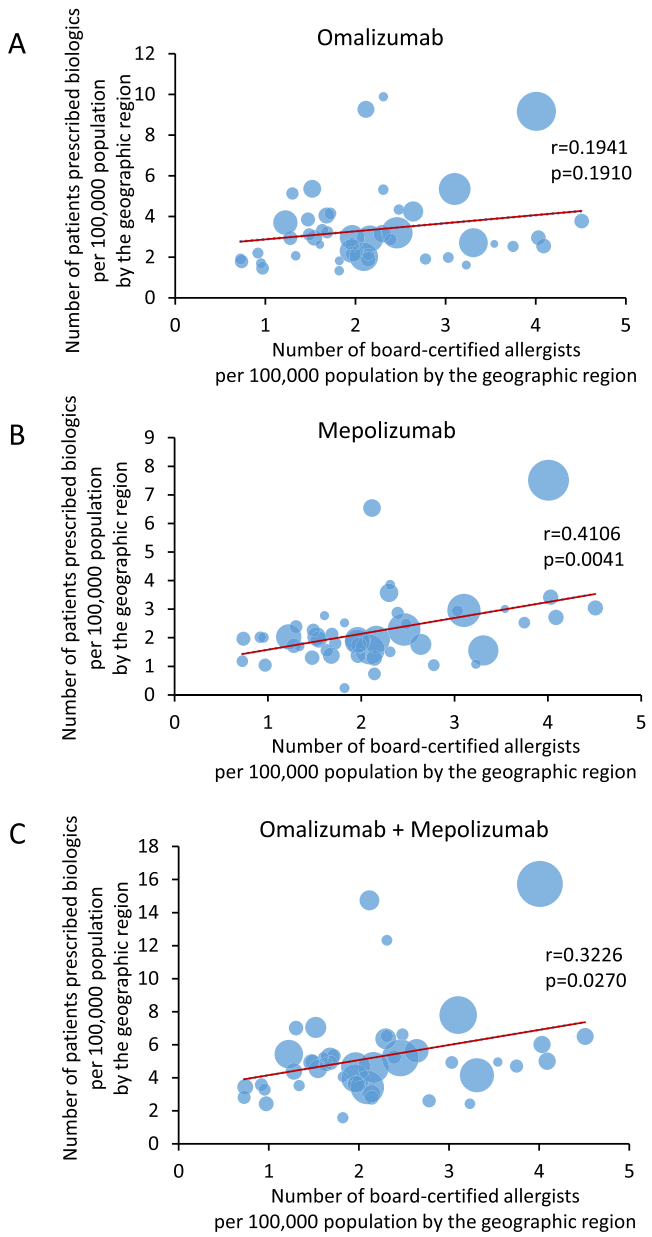

Fig. 5. The correlation between the number of patients prescribed biologics and board-certified allergists. The numbers of patients prescribed omalizumab (A), mepolizumab (B), and omalizumab or mepolizumab (C) patients per 100,000 people by geographic region were counted. The number of board-certified allergists (internal medicine and pediatrics) in 2017 was counted. The bubble size and the population in each prefecture are proportional.

cannot be ruled out. The NDB used in this study does not include welfare recipients or short-term foreign residents. However, these populations represent approximately 1.68 % of the population and are not expected to impact the results significantly [30]. The NDB did not include the detailed laboratory or medical data of each patient. Therefore, we could not analyze the detailed patient characteristics, asthma phenotypes, levels of type 2 biomarkers, or therapeutic effects. In this study, the prescription rate for biologics might need to be evaluated based on the number of prescriptions for patients with severe asthma. However, since the NDB analysis does not include medical data, it is impossible to determine asthma control status. Therefore, the number of patients with severe asthma cannot be calculated.

5. Conclusions

In conclusion, the number of patients prescribed biologics for asthma treatment was approximately paralleled by the number of adult patients with asthma, according to sex and age groups (Supplementary Fig. 2). However, the proportion of biologics utilization plummeted in their sixties, especially among females, and varied widely by region. This indicates the need for eliminating the regional disparities in asthma treatment by specialists for providing appropriate medical care to patients with severe asthma.

Authors' contributions

KKan and KKai, and ENGAGE NDB Task Force designed the study. KKan, KKai, and HO performed data analysis and wrote the manuscript. TN, YN, TM, and TIma contributed to the data acquisition and analysis. KM, TA, HM, and MT contributed to the study management and data interpretation. All the authors have read and approved the final version of the manuscript.<a name = "Line_manuscript_69">

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Data availability statement

The datasets generated for this study are available on request to the corresponding author.

Declaration of competing interest

YN received consulting fees and an honorarium for speakers bureaus from Novo Nordisk, Daiichi Sankyo, and Sanofi. TM received consulting fees from the Health Insurance Claims Review & Reimbursement services. HM received a research grant from GlaxoSmithKline Japan that was unrelated to the submitted work. TIno received a research grant from Johnson & Johnson Vision Care, SEED Co., Ltd., Novartis Pharma K·K., and Kowa Company, Ltd that was unrelated to the submitted work, consulting fees from Santen Pharmaceutical Co., Ltd. and InnoJin, Inc., and stock or stock options from InnoJin, Inc. MF received an honorarium for speakers bureaus from Sanofi K·K., Kyorin Pharmaceutical Co., Ltd., and Novartis Pharma Co., Ltd. The other authors have no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.resinv.2023.11.003.

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