Therapeutics and Clinical Risk Management

Dovepress
open access to scientific and medical research

Open Access Full Text Article

ORIGINAL RESEARCH

Biologic Disease-Modifying and Other Anti-Rheumatic Drugs Use in Patients with Moderate-to-Severe Juvenile Idiopathic Arthritis Based on a Japanese Nationwide Claims Database

Takeo Hata[1], Atsushi Hirata[2], Ryosuke Ota[2], Keiko Hosohata[3], Masami Nishihara[1], Masashi Neo[1], Takahiro Katsumata[1]

[1]Department of Pharmacy, Osaka Medical and Pharmaceutical University Hospital, Takatsuki, Osaka, Japan; [2]Department of Pharmacy, Kindai University Nara Hospital, Ikoma, Nara, Japan; [3]Education and Research Center for Clinical Pharmacy, Osaka Medical and Pharmaceutical University, Takatsuki, Osaka, Japan

Correspondence: Keiko Hosohata, Education and Research Center for Clinical Pharmacy, Osaka Medical and Pharmaceutical University, 4-20-1 Nasahara, Takatsuki, Osaka, 569-1094, Japan, Tel +81-72-690-1271, Fax +81-72-690-1023, Email hosohata@gly.oups.ac.jp

Purpose: Biologic disease-modifying anti-rheumatic drugs (bDMARDs) are highly effective and safe against juvenile idiopathic arthritis (JIA), which is classified into systemic JIA (sJIA) and the other JIA categories (non-sJIA) according to differences in clinical symptoms and pathophysiology. The purpose of the current study was to investigate trends in patterns of prescribing bDMARDs for moderate-to-severe JIA using a relatively large sample size in Japan.

Patients and Methods: A descriptive epidemiological study based on a nationwide claims database in Japan was conducted from 2012 to 2018 using the "JMDC Claims Database" to explain annual changes based on the number of patients prescribed bDMARDs. Study drugs were identified based on the Anatomical Therapeutic Chemical codes, such as methotrexate, glucocorticoids, non-steroidal anti-inflammatory drugs, and bDMARDs.

Results: From a database of 6,862,244 patients, the following exclusion criteria were applied: aged ≥16 years, without "M08" in their ICD-10 code as disease, and missing the information of prescription date in the database during the study period, resulting in a final number of 111 JIA patients. We found an increasing trend for adalimumab and tocilizumab and a decreasing trend for methotrexate. Differences in medication use between sJIA and non-sJIA patients were also evident, being consistent with national and international guidelines.

Conclusion: Although the introduction of bDMARDs has markedly improved the efficacy of JIA therapy, there are still many short- and long-term safety issues to be examined, including the risk of infection and potential risk of associated malignancy. Future studies are needed to clarify these issues.

Keywords: arthritis, juvenile, antirheumatic agents, biological products, database

Introduction

Juvenile idiopathic arthritis (JIA) is the most chronic inflammatory disease that develops in childhood, defined by the International League of Associations for Rheumatology (ILAR) as chronic arthritis of unknown etiology beginning before the 16th birthday and persisting for at least six weeks when other known causes are excluded.[1] The prevalence of JIA is 10–15 cases per 100,000 children in Japan. The incidence of each JIA category is different according to countries and areas.[2] The JIA symptoms are accompanied by swelling and pain of joints due to persistent inflammation, resulting in tissue destruction and fibrosis over time. JIA is an umbrella term for a heterogeneous group of conditions classified according to ILAR, and the current

Received: 23 May 2022
Accepted: 8 August 2022
Published: 24 August 2022

classification of JIA was proposed,[3] with an initial revision in 1997.[1] This classification includes seven categories of JIA which mainly fall into two types according to differences in clinical symptoms and pathophysiology, namely systemic JIA (sJIA) and the other six JIA categories. The latter consist of oligoarthritis, rheumatoid factor-negative polyarthritis, rheumatoid factor-positive polyarthritis, psoriatic arthritis, enthesitis-related arthritis, and undifferentiated arthritis, and are often considered as "articular-type JIA" (non-sJIA) in clinical practice in Japan.[1] Like other inflammatory diseases, the immunological etiology of JIA involves a multiphasic dysregulated immune system, affecting both innate and adaptive branches. Some inflammatory cytokines, such as interleukin (IL)-1, IL-6, IL-18, and tumor necrosis factor (TNF)-α, are centrally involved throughout this multistep and multiphase cascade reaction as a whole, leading to this complex pathology.[4,5] In particular, IL-6 is a pleiotropic cytokine that mediates the acute-phase response.[6]

Traditionally, the initial treatment strategy for JIA is methylprednisolone pulse therapy for sJIA and non-steroidal anti-inflammatory drugs (NSAIDs) and methotrexate for non-sJIA.[4] Since JIA develops during the growth phase, delayed treatment may lead to irreversible dysfunction, and early treatment can prevent joint dysfunction and failure to thrive. However, if these treatments are inadequate, it is necessary to consult pediatric rheumatologists; the early introduction of biologic disease-modifying anti-rheumatic drugs (bDMARDs) should be considered for such cases. Although it is very important to clarify whether the actual clinical treatment is consistent with the guideline recommendations in order to promote the appropriate use of therapeutic agents, there has been no report focusing on prescribing trends for treatment with bDMARDs for moderate-to-severe JIA in Japan. In addition, because JIA is a rare disease, it is a population which has a high likelihood for off-label drug use, and biologics not approved for JIA are prescribed as treatment options.[7] Therefore, the purpose of the current study was to analyze the trends in patterns of prescribing bDMARDs and other anti-rheumatic drugs for moderate-to-severe JIA using a relatively large sample in Japan.

Methods

Study Design

A descriptive epidemiological study based on a nationwide claims database in Japan was conducted.

Data Source

The data source was the "JMDC Claims Database" (JMDC Inc., Tokyo, Japan) from 2012 to 2018 in Japan. The database consists of medical, dental, and prescription claims information for enrollees of multiple society-managed health insurances and their dependents. The 6.8 million people in this national claims database represent approximately 5.4% of the total Japanese population. Since the subscribers in this database are mainly working-age people, it does not include patients over 75 years old, and the number of patients over 65 years old is also limited. The database provides information on patient demographics, disease names, and medications. Disease and drug names are coded by the International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10) and the Anatomical Therapeutic and Chemical (ATC) classification system of the World Health Organization.

Study Population

The following exclusion criteria were established for this study: age ≥16 years, other than JIA. We excluded patients aged ≥16 years because JIA is defined as arthritis of unknown etiology that begins before the 16th birthday.[1] Patients with JIA were identified by coding "M08" in ICD-10. Patients with missing data on the prescription date of the drug under investigation were also excluded. JIA is broadly classified into sJIA and non-sJIA according to the presence or absence of systemic inflammation,[4,8] and treatment algorithms differ between these two types.[4,9] Also, the categories of oligoarticular and polyarticular JIA are viewed as being on a spectrum of the same disease,[9] so this study also categorized them as sJIA and non-sJIA. sJIA was identified by "M082" in ICD-10, and the other types were defined as non-sJIA.

Study Drugs

The bDMARDs indicated for JIA in Japan and their approval dates are as follows: abatacept (February 2018), adalimumab (July 2011), canakinumab (July 2018), etanercept (July 2009), and tocilizumab (April 2008). The dates of

approval in Japan for golimumab and infliximab for off-label use in JIA are July 2011 and January 2002, respectively. These were identified by L04A in ATC. Other immunosuppressants were likewise identified by L04A. In addition, glucocorticoids and NSAIDs used in JIA were identified by H02AB and M01A, respectively. Janus kinase inhibitors are not approved for patients with JIA in Japan and are therefore not included in this study.

Ethical Considerations

All procedures for this study involving human subjects were performed in accordance with the ethical standards of the Institutional Research Board and the 1964 Declaration of Helsinki and its subsequent amendments, as well as comparable ethical standards. Because this was a retrospective observational study with no interventions and no invasions, and because the database used was anonymized prior to the researcher's availability and could not be used to identify individuals, patient explanation and consent were waived. This study was approved by the Ethics Committee of Osaka Medical and Pharmaceutical University (Approval ID: 2762-1) on August 6, 2019.

Statistical Analysis

The number of patients and percentage of users in each year were determined for each drug. The database included 111 patients with moderate-to-severe JIA, but the cumulative number of patients was 398 because of the presence of those belonging to multiple years. The Cochran–Armitage trend test was used to test the prescribing trend for each drug. All *P*-values are reported with a two-tailed test, and the significance level was set at 5%. Statistical analyses were performed using R version 4.0.2 (R Development Core Team, Vienna, Austria).

Results

Participants

From a database of 6,862,244 patients, we extracted 9704 patients who were prescribed bDMARDs at least once during the observation period. In addition, we excluded 9349 patients aged ≥16 years, 242 patients without "M08" in ICD-10, and 2 patients whose prescription date was missing, resulting in a final sample of 111 moderate-to-severe JIA patients (Figure 1). In addition, 1,488,202 patients under 16 years of age were included in the base population of 6,862,244. Participants' annual background is shown in Table 1. Patients who were prescribed bDMARDs for multiple years were counted each year, and when switched to other bDMARDs, they were counted in each bDMARDs. Therefore, the number of patients was 111, and the total number of patients was 398. In 2018, females accounted for 64.3% of the total JIA population, being 12.5 (8–15) years of age. By disease type in sJIA patients, 51.6% were female and they were 11 (8–13) years of age, but in non-sJIA patients,

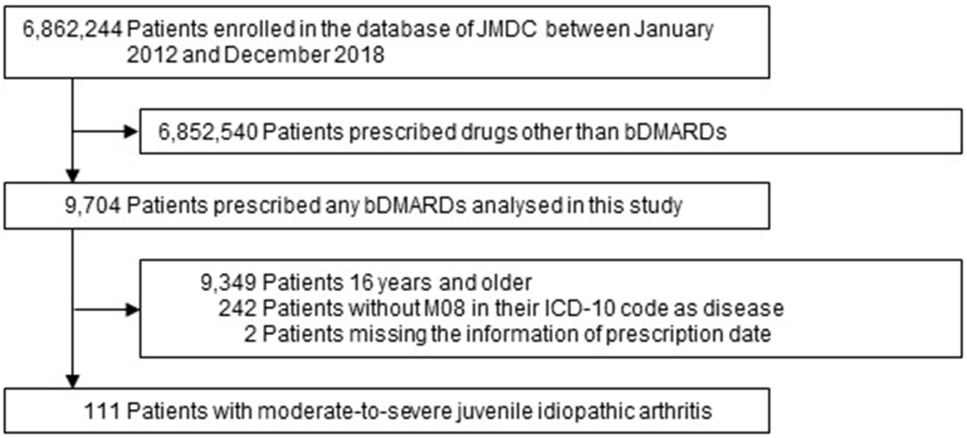

Figure 1 Flow diagram to construct the study cohort of juvenile idiopathic arthritis patients.
Abbreviations: bDMARDs, biological disease-modifying anti-rheumatic drugs; ICD-10, International Statistical Classification of Diseases and Related Health Problems, 10th Revision.

Table 1 Demographics of Patients with Juvenile Idiopathic Arthritis Prescribed bDMARDs

Classification	Characteristics	2012	2013	2014	2015	2016	2017	2018	Total
	Patients, n	12	17	9	24	20	18	11	111
	Prescribed bDMARDs, n	12	29	36	59	74	90	98	398[a]
Overall	Sex, n (%)								
	Female	10 (83.3)	21 (72.4)	26 (72.2)	40 (67.8)	49 (66.2)	59 (65.6)	63 (64.3)	268 (67.3)
	Male	2 (16.7)	8 (27.6)	10 (27.8)	19 (32.2)	25 (33.8)	31 (34.4)	35 (35.7)	130 (32.7)
	Age, Median (IQR)	10 (7–14)	10 (6–13)	9.5 (4–14)	11 (6–14)	11.5 (7–14)	12 (8–14)	12.5 (8–15)	11.5 (7–14)
sJIA	Sex, n (%)								
	Female	1 (100)	5 (62.5)	6 (54.5)	9 (47.4)	13 (50.0)	15 (50.0)	16 (51.6)	65 (51.6)
	Male	0 (0)	3 (37.5)	5 (45.5)	10 (52.6)	13 (50.0)	15 (50.0)	15 (48.4)	61 (48.4)
	Age, Median (IQR)	14 (14–14)	10 (4–15)	8 (4–15)	9 (5–12)	10 (6–12)	11 (8–13)	11 (8–13)	10.5 (7–13)
Non-sJIA	Sex, n (%)								
	Female	9 (81.8)	16 (76.2)	20 (80.0)	31 (77.5)	36 (75.0)	44 (73.3)	47 (70.1)	203 (74.6)
	Male	2 (18.2)	5 (23.8)	5 (20.0)	9 (22.5)	12 (25.0)	16 (26.7)	20 (29.9)	69 (25.4)
	Age, Median (IQR)	9 (7–13)	10 (6–13)	11 (6–14)	12 (7–14)	12.5 (8–15)	12.5 (7–15)	13 (7–16)	12 (7–15)

Notes: [a]The number of patients with juvenile idiopathic arthritis prescribed biologic agents was 111, and the cumulative total number of patients was 398 because patients were enrolled in the database of multiple years.
Abbreviations: bDMARDs, biological disease-modifying anti-rheumatic drugs; IQR, interquartile range; sJIA, systemic juvenile idiopathic arthritis.

70.1% were female and they were 13 (7–16) years of age, with no sex difference in sJIA, whereas the proportion of females was higher in non-JIA. No differences in age were observed.

Prescribing Trend for JIA

The mean and standard deviation of the number of drugs prescribed for the patients with JIA during the study period was 5.1±2.8. Table 2 shows the annual change in the proportion of drug use among all moderate-to-severe JIA patients. The percentage of prescriptions for adalimumab and tocilizumab showed a significant increase, whereas the percentage of prescriptions for methotrexate and flurbiprofen showed a significant decrease. Focusing on 2018, tocilizumab and adalimumab were prescribed in 42.9 and 29.6% of all JIA patients, respectively. Glucocorticoids accounted for 41.8% with all injectable prescriptions and 52.0% with all oral prescriptions, with prednisolone (oral) accounting for the highest percentage at 45.9%. Among immunosuppressants, methotrexate accounted for 51.0%, among NSAIDs, and ibuprofen and loxoprofen sodium accounted for 24.5 and 17.3%, respectively. For other off-label biological products for JIA in Japan, rituximab was prescribed to one patient in 2017 and 2018, respectively. No patients used certolizumab pegol and ustekinumab. Rilonacept and anakinra have not been released in Japan.

Prescribing Trend for sJIA

Annual trends in the percentage of drug use in sJIA are shown in Table 3. A significant increase in the percentage of prescriptions was observed for adalimumab. Regarding 2018, tocilizumab use was particularly high in sJIA patients with 71.0% and 22.6% for tocilizumab and adalimumab, respectively. Canakinumab, which is only covered for sJIA patients showing an inadequate response or poor tolerability to existing therapies such as tocilizumab, was 9.7%. Glucocorticoids were prescribed in 58.1% among all sJIA patients with all injectables and 87.1% with all orals, with prednisolone (oral) being prescribed in a particularly high percentage (71.0%). For immunosuppressants, methotrexate, tacrolimus hydrate, and ciclosporin were prescribed in 38.7, 22.6, and 19.4% of sJIA patients, respectively. The proportion of immunosuppressants other than methotrexate was high in patients with sJIA. Among NSAIDs, ibuprofen and loxoprofen sodium were prescribed in 29.0 and 12.9%, respectively.

Prescribing Trend for Non-sJIA

Table 3 shows the annual change in drug use in non-sJIA patients. A significant increase in the percentage of prescriptions for adalimumab and tocilizumab was noted, whereas a significant decrease in the percentage of prescriptions for methotrexate and flurbiprofen was observed. In 2018, prescription rates were higher for adalimumab and tocilizumab at 32.8 and 29.9%, respectively, and for etanercept and infliximab at 14.9 and 11.9%, respectively, in non-sJIA. Glucocorticoids were prescribed for 34.3% with all injectables and 35.8% with all orals, including 34.3% for prednisolone (oral), both of which were clearly lower than the proportions in sJIA patients. Among immunosuppressants, 56.7% of non-sJIA patients were prescribed methotrexate, higher than in sJIA. Among NSAIDs, ibuprofen and loxoprofen sodium were used in 22.4 and 19.4% of non-sJIA patients, respectively.

Discussion

In this study, we analyzed prescribing trends of bDMARDs and other anti-rheumatic drugs in patients with moderate-to-severe JIA using a nationwide Japanese claims database. The results showed that the use of bDMARDs increased annually, and that the use of each agent for sJIA and non-sJIA was generally consistent with recommendations in the guidelines. This is the first study in Japan to investigate prescribing for moderate-to-severe JIA using nationwide claims data.

The prevalence of JIA in Japan is 10–15 per 100,000 children.[4] According to Japanese government statistics (https://www.e-stat.go.jp/dbview?sid=0003171241), there were 16,954,000 children under the age of 16 (0–15 years total) as of 2016. From this, it is estimated that there are 1695 JIA cases in Japan as a whole. Thus, it is estimated that 91.53 JIA cases are included in the "JMDC" data, which covers about 5.4% (6.8 million people) of the Japanese population. This is very close to the value in Table 1. In North America and Europe, sJIA is estimated to be 5–15%, whereas in Japan it is 41.7 or 8–50%.[4] In the patients in this study, sJIA was also about 30%, higher than reported values in North America and

https://doi.org/10.2147/TCRM.S375890 DovePress

Table 2 Annual Proportions in Each Drugs Prescribed for Patients with Juvenile Idiopathic Arthritis Over Time

	2012 n = 12	2013 n = 29	2014 n = 36	2015 n = 59	2016 n = 74	2017 n = 90	2018 n = 98	*P*-value
bDMARDs, n (%)								
Abatacept	0 (0)	0 (0)	1 (2.8)	1 (1.7)	1 (1.4)	0 (0)	2 (2.0)	0.8420
Adalimumab	0 (0)	3 (10.3)	6 (16.7)	10 (16.9)	11 (14.9)	24 (26.7)	29 (29.6)	0.0006
Canakinumab	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	3 (3.1)	N.A.
Etanercept	3 (25.0)	4 (13.8)	5 (13.9)	7 (11.9)	13 (17.6)	14 (15.6)	10 (10.2)	0.4026
Golimumab	0 (0)	0 (0)	0 (0)	0 (0)	1 (1.4)	1 (1.1)	2 (2.0)	0.1536
Infliximab	0 (0)	1 (3.4)	2 (5.6)	4 (6.8)	6 (8.1)	7 (7.8)	10 (10.2)	0.1035
Tocilizumab	2 (16.7)	7 (24.1)	13 (36.1)	22 (37.3)	29 (39.2)	37 (41.1)	42 (42.9)	0.0265
Glucocorticoids, n (%)								
Total for injectable formulations	5 (41.7)	11 (37.9)	18 (50.0)	29 (49.2)	32 (43.2)	41 (45.6)	41 (41.8)	0.8162
Betamethasone sodium phosphate	1 (8.3)	1 (3.4)	3 (8.3)	2 (3.4)	3 (4.1)	4 (4.4)	5 (5.1)	0.7857
Dexamethasone palmitate	0 (0)	1 (3.4)	2 (5.6)	4 (6.8)	6 (8.1)	9 (10.0)	7 (7.1)	0.2290
Dexamethasone sodium phosphate	2 (16.7)	2 (6.9)	4 (11.1)	3 (5.1)	5 (6.8)	6 (6.7)	8 (8.2)	0.6126
Hydrocortisone sodium phosphate	0 (0)	0 (0)	0 (0)	2 (3.4)	1 (1.4)	1 (1.1)	1 (1.0)	0.8420
Hydrocortisone sodium succinate	0 (0)	2 (6.9)	5 (13.9)	5 (8.5)	5 (6.8)	7 (7.8)	10 (10.2)	0.6489
Methylprednisolone sodium succinate	1 (8.3)	2 (6.9)	2 (5.6)	5 (8.5)	5 (6.8)	5 (5.6)	4 (4.1)	0.3693
Prednisolone sodium succinate	1 (8.3)	3 (10.3)	2 (5.6)	7 (11.9)	6 (8.1)	8 (8.9)	5 (5.1)	0.4067
Triamcinolone acetonide	0 (0)	0 (0)	0 (0)	1 (1.7)	1 (1.4)	1 (1.1)	1 (1.0)	0.5927
Total for oral formulations	6 (50.0)	14 (48.3)	21 (58.3)	35 (59.3)	43 (58.1)	45 (50.0)	51 (52.0)	0.6856
Betamethasone	0 (0)	1 (3.4)	0 (0)	0 (0)	2 (2.7)	1 (1.1)	0 (0)	0.5129
Hydrocortisone	0 (0)	0 (0)	2 (5.6)	3 (5.1)	4 (5.4)	4 (4.4)	4 (4.1)	0.5432
Methylprednisolone	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1.1)	2 (2.0)	0.0964
Prednisolone	6 (50.0)	13 (44.8)	19 (52.8)	32 (54.2)	37 (50.0)	39 (43.3)	45 (45.9)	0.4196
Immunosuppressants, n (%)								
Azathioprine	1 (8.3)	1 (3.4)	1 (2.8)	4 (6.8)	4 (5.4)	3 (3.3)	3 (3.1)	0.4765
Ciclosporin	1 (8.3)	2 (6.9)	2 (5.6)	2 (3.4)	4 (5.4)	5 (5.6)	6 (6.1)	0.9891
Methotrexate	10 (83.3)	18 (62.1)	22 (61.1)	33 (55.9)	43 (58.1)	49 (54.4)	50 (51.0)	0.0463
Mycophenolate mofetil	0 (0)	0 (0)	0 (0)	2 (3.4)	2 (2.7)	4 (4.4)	4 (4.1)	0.1032
Tacrolimus hydrate	0 (0)	1 (3.4)	3 (8.3)	6 (10.2)	8 (10.8)	9 (10.0)	8 (8.2)	0.3881
NSAIDs, n (%)								
Flurbiprofen	4 (33.3)	4 (13.8)	4 (11.1)	5 (8.5)	4 (5.4)	3 (3.3)	6 (6.1)	0.0020
Ibuprofen	1 (8.3)	6 (20.7)	9 (25.0)	10 (16.9)	16 (21.6)	22 (24.4)	24 (24.5)	0.2656
Loxoprofen sodium	3 (25.0)	1 (3.4)	4 (11.1)	8 (13.6)	11 (14.9)	10 (11.1)	17 (17.3)	0.3730
Naproxen	0 (0)	0 (0)	3 (8.3)	6 (10.2)	5 (6.8)	7 (7.8)	7 (7.1)	0.3786

Note: *P*-values were calculated with the Cochran–Armitage trend test.

Abbreviations: bDMARDs, biological disease-modifying anti-rheumatic drugs; N.A., not applicable; NSAIDs, non-steroidal anti-inflammatory drugs.

Table 3 Annual Proportions in Each Drugs Prescribed for Patients with Systemic Juvenile Idiopathic Arthritis or Non-Systemic Juvenile Idiopathic Arthritis Over Time

	Systemic Juvenile Idiopathic Arthritis								Non-Systemic Juvenile Idiopathic Arthritis							
	2012 n = 1	2013 n = 8	2014 n = 11	2015 n = 19	2016 n = 26	2017 n = 30	2018 n = 31	*P*-value	2012 n = 11	2013 n = 21	2014 n = 25	2015 n = 40	2016 n = 48	2017 n = 60	2018 n = 67	*P*-value
bDMARDs, n (%)																
Abatacept	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	N.A.	0 (0)	0 (0)	1 (4.0)	1 (2.5)	1 (2.1)	0 (0)	2 (3.0)	0.7855
Adalimumab	0 (0)	0 (0)	1 (9.1)	2 (10.5)	2 (7.7)	6 (20.0)	7 (22.6)	0.0362	0 (0)	3 (14.3)	5 (20.0)	8 (20.0)	9 (18.8)	18 (30.0)	22 (32.8)	0.0037
Canakinumab	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	3 (9.7)	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	0 (0)	N.A.
Etanercept	0 (0)	0 (0)	0 (0)	1 (5.3)	2 (7.7)	2 (6.7)	0 (0)	0.9794	3 (27.3)	4 (19.0)	5 (20.0)	6 (15.0)	11 (22.9)	12 (20.0)	10 (14.9)	0.5091
Golimumab	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (3.2)	0.2376	0 (0)	0 (0)	0 (0)	0 (0)	1 (2.1)	1 (1.7)	1 (1.5)	0.3143
Infliximab	0 (0)	0 (0)	0 (0)	1 (5.3)	2 (7.7)	2 (6.7)	2 (6.5)	0.3488	0 (0)	1 (4.8)	2 (8.0)	3 (7.5)	4 (8.3)	5 (8.3)	8 (11.9)	0.1611
Tocilizumab	1 (100)	4 (50.0)	8 (72.7)	13 (68.4)	18 (69.2)	21 (70.0)	22 (71.0)	0.6074	1 (9.1)	3 (14.3)	5 (20.0)	9 (22.5)	11 (22.9)	16 (26.7)	20 (29.9)	0.0446
Glucocorticoids, n (%)																
Total for injectable formulations	1 (100)	5 (62.5)	8 (72.7)	15 (78.9)	18 (69.2)	21 (70.0)	18 (58.1)	0.2813	4 (36.4)	6 (28.6)	10 (40.0)	14 (35.0)	14 (29.2)	20 (33.3)	23 (34.3)	0.9417
Betamethasone sodium phosphate	0 (0)	0 (0)	2 (18.2)	1 (5.3)	0 (0)	2 (6.7)	1 (3.2)	0.5705	1 (9.1)	1 (4.8)	1 (4.0)	1 (2.5)	3 (6.3)	2 (3.3)	4 (6.0)	0.9814
Dexamethasone palmitate	0 (0)	1 (12.5)	1 (9.1)	3 (15.8)	4 (15.4)	4 (13.3)	3 (9.7)	0.8733	0 (0)	0 (0)	1 (4.0)	1 (2.5)	2 (4.2)	5 (8.3)	4 (6.0)	0.0995
Dexamethasone sodium phosphate	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (3.2)	0.2376	2 (18.2)	2 (9.5)	4 (16.0)	3 (7.5)	5 (10.4)	6 (10.0)	7 (10.4)	0.5993
Hydrocortisone sodium phosphate	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	N.A.	0 (0)	0 (0)	0 (0)	2 (5.0)	1 (2.1)	1 (1.7)	1 (1.5)	0.7855
Hydrocortisone sodium succinate	0 (0)	1 (12.5)	3 (27.3)	4 (21.1)	4 (15.4)	6 (20.0)	7 (22.6)	0.7246	0 (0)	1 (4.8)	2 (8.0)	1 (2.5)	1 (2.1)	1 (1.7)	3 (4.5)	0.8615
Methylprednisolone sodium succinate	1 (100)	2 (25.0)	1 (9.1)	4 (21.1)	5 (19.2)	3 (10.0)	3 (9.7)	0.0917	0 (0)	0 (0)	1 (4.0)	1 (2.5)	0 (0)	2 (3.3)	1 (1.5)	0.7855
Prednisolone sodium succinate	0 (0)	1 (12.5)	1 (9.1)	3 (15.8)	5 (19.2)	6 (20.0)	3 (9.7)	0.9317	1 (9.1)	2 (9.5)	1 (4.0)	4 (10.0)	1 (2.1)	2 (3.3)	2 (3.0)	0.1094
Triamcinolone acetonide	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	N.A.	0 (0)	0 (0)	0 (0)	1 (2.5)	1 (2.1)	1 (1.7)	1 (1.5)	0.5563
Total for oral formulations	1 (100)	3 (37.5)	9 (81.8)	19 (100)	21 (80.8)	24 (80.0)	27 (87.1)	0.1709	5 (45.5)	11 (52.4)	12 (48.0)	16 (40.0)	22 (45.8)	21 (35.0)	24 (35.8)	0.1083
Betamethasone	0 (0)	0 (0)	0 (0)	0 (0)	1 (3.8)	0 (0)	0 (0)	0.9056	0 (0)	1 (4.8)	0 (0)	0 (0)	1 (2.1)	1 (1.7)	0 (0)	0.5141
Hydrocortisone	0 (0)	0 (0)	1 (9.1)	2 (10.5)	2 (7.7)	3 (10.0)	3 (9.7)	0.5411	0 (0)	0 (0)	1 (4.0)	1 (2.5)	2 (4.2)	1 (1.7)	1 (1.5)	0.9875
Methylprednisolone	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (3.3)	2 (6.5)	0.0922	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	N.A.
Prednisolone	1 (100)	3 (37.5)	8 (72.7)	17 (89.5)	18 (69.2)	20 (66.7)	22 (71.0)	0.8243	5 (45.5)	10 (47.6)	11 (44.0)	15 (37.5)	19 (39.6)	19 (31.7)	23 (34.3)	0.1352
Immunosuppressants, n (%)																
Azathioprine	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (3.3)	1 (3.2)	0.2242	1 (9.1)	1 (4.8)	1 (4.0)	4 (10.0)	4 (8.3)	2 (3.3)	2 (3.0)	0.2995
Ciclosporin	1 (100)	1 (12.5)	1 (9.1)	2 (10.5)	3 (11.5)	4 (13.3)	6 (19.4)	0.7776	0 (0)	1 (4.8)	1 (4.0)	0 (0)	1 (2.1)	1 (1.7)	0 (0)	0.2548
Methotrexate	0 (0)	3 (37.5)	6 (54.5)	7 (36.8)	13 (50.0)	14 (46.7)	12 (38.7)	0.9963	10 (90.9)	15 (71.4)	16 (64.0)	26 (65.0)	30 (62.5)	35 (58.3)	38 (56.7)	0.0311
Mycophenolate mofetil	0 (0)	0 (0)	0 (0)	0 (0)	1 (3.8)	2 (6.7)	2 (6.5)	0.1329	0 (0)	0 (0)	0 (0)	2 (5.0)	1 (2.1)	2 (3.3)	2 (3.0)	0.3723
Tacrolimus hydrate	0 (0)	0 (0)	1 (9.1)	3 (15.8)	3 (11.5)	6 (20.0)	7 (22.6)	0.0733	0 (0)	1 (4.8)	2 (8.0)	3 (7.5)	5 (10.4)	3 (5.0)	1 (1.5)	0.4630
NSAIDs, n (%)																
Flurbiprofen	0 (0)	1 (12.5)	1 (9.1)	2 (10.5)	2 (7.7)	2 (6.7)	2 (6.5)	0.5467	4 (36.4)	3 (14.3)	3 (12.0)	3 (7.5)	2 (4.2)	1 (1.7)	4 (6.0)	0.0010
Ibuprofen	0 (0)	2 (25.0)	2 (18.2)	2 (10.5)	4 (15.4)	5 (16.7)	9 (29.0)	0.3311	1 (9.1)	4 (19.0)	7 (28.0)	8 (20.0)	12 (25.0)	17 (28.3)	15 (22.4)	0.4279
Loxoprofen sodium	0 (0)	1 (12.5)	2 (18.2)	2 (10.5)	2 (7.7)	3 (10.0)	4 (12.9)	0.9188	3 (27.3)	0 (0)	2 (8.0)	6 (15.0)	9 (18.8)	7 (11.7)	13 (19.4)	0.2630
Naproxen	0 (0)	0 (0)	3 (27.3)	2 (10.5)	3 (11.5)	1 (3.3)	2 (6.5)	0.3063	0 (0)	0 (0)	0 (0)	4 (10.0)	2 (4.2)	6 (10.0)	5 (7.5)	0.0811

Notes: *P*-values were calculated with the Cochran–Armitage trend test.

Abbreviations: bDMARDs, biological disease-modifying anti-rheumatic drugs; N.A., not applicable; NSAIDs, non-steroidal anti-inflammatory drugs.

https://doi.org/10.2147/TCRM.S375890 DovePress

Europe. There is no sex difference in the prevalence of sJIA, whereas non-sJIA is more than twice as common in females.[4,9] The present study is also consistent with these reports regarding sex differences in prevalence.

Prescribing trend analysis of bDMARDs in all moderate-to-severe JIA patients showed a significant increase in adalimumab and tocilizumab, but a decrease in methotrexate. These findings are consistent with our previously reported results of a prescribing trend analysis in rheumatoid arthritis (RA) patients.[10] The American College of Rheumatology (ACR) and Japan College of Rheumatology recommend aggressive treatment with bDMARDs.[4,11] Although etanercept was the most commonly prescribed bDMARD for JIA in 2012,[12,13] adalimumab, which is indicated for non-sJIA, and tocilizumab, which is indicated for both sJIA and non-sJIA, have become more common with expansion of the evidence-based selection of bDMARDs for JIA.[14] The ACR recommendations for non-sJIA published in 2019 show that adalimumab has a higher level of evidence than other bDMARDs.[15] Previous study comparing TNF-α inhibitor to non-TNF-α inhibitor for non-sJIA found that TNF-α inhibitor was more effective.[16] The results of our study also showed that adalimumab, etanercept, and infliximab were used in high proportions in non-sJIA. Early introduction of tocilizumab has been reported to be beneficial in patients with sJIA.[17] Additionally, adalimumab, etanercept, and tocilizumab showed comparable efficacy against polyarticular JIA in non-sJIA, with tocilizumab reported to have the lowest discontinuation rate.[18] We consider that these findings support the increasing use of bDMARDs, especially in the proportion of patients treated with adalimumab and tocilizumab. Patil et al reported that methotrexate-induced nausea is six times more common in adolescents than in adults.[19] Up to one-third of patients with JIA may experience side effects with methotrexate monotherapy.[20] This poor tolerability is considered to be one of the reasons for the decreasing tendency of methotrexate. In our study, we also observed the use of golimumab and infliximab, which are not currently approved for JIA in Japan. Although bDMARDs are effective in most cases, some children do not respond to treatment and continue to suffer from active symptoms. In these cases, bDMARDs not approved for JIA are introduced into the treatment.[7,21] Several reports suggest the efficacy and safety of golimumab[22–24] and infliximab[25–29] for non-sJIA. These findings support the inclusion of the off-label use of bDMARDs in our study.

In the percentage of bDMARDs used for non-sJIA, no drugs stood out among TNF-α and IL-6 inhibitors. In contrast, the use of bDMARDs for sJIA was distinctive. Tocilizumab, an IL-6 inhibitor, is the mainstay of treatment for sJIA, with a rate of 71% in 2018. Canakinumab (IL-1 inhibitor), approved that year only for sJIA patients with an inadequate response to existing therapies such as tocilizumab, was used in 9.7% of cases. This suggests that refractory or intolerant cases comprised approximately 9.7% of sJIA patients. Drugs with later approval dates will be used for new patients and patients who are concerned about the efficacy or safety of existing therapies, so the rate of use will increase moderately. The TNF-α inhibitors adalimumab, infliximab, and golimumab, which have not been approved for sJIA, were also used. These may be options in patients showing active disease refractory to IL-1 or IL-6 inhibitors.

Many patients with sJIA had to be treated with chronic glucocorticoids, sometimes for years, which caused many side effects and growth disturbances.[9] The outlook for the management of sJIA has evolved radically over the past two decades from a heavy reliance on glucocorticoids to the early introduction of bDMARDs against IL-1 and IL-6 for targeted therapy with no or minimal use of glucocorticoids.[9] The introduction of bDMARDs to treat JIA has markedly improved disease outcomes and reduced the use of the more deleterious systemic glucocorticoids.[30] We found no significant decrease in glucocorticoids in this study. This may be due to the short observation period, starting in 2012; because several bDMARDs were already on the market in 2012, we could not complement the decrease in glucocorticoids. However, glucocorticoids remain a mainstay of treatment for sJIA patients due to their high use, compared with 30–40% for non-sJIA.

Regarding immunosuppressants, in addition to methotrexate, the calcineurin inhibitors tacrolimus hydrate and ciclosporin were also used in a high percentage of sJIA patients. Methotrexate and ciclosporin have been reported to show limited sustained efficacy after systemic symptoms have resolved in sJIA.[4] On the other hand, sJIA has been associated with macrophage activation syndrome (MAS), a life-threatening complication requiring urgent treatment.[31] In some patients with MAS, the concomitant use of calcineurin inhibitors in addition to bDMARDs and glucocorticoids may be necessary to control MAS.[32] These results suggest that patients using calcineurin inhibitors not approved for JIA captured in our study could be those with complicated MAS. The long-term efficacy and safety of methotrexate for non-sJIA have been well-established and it is used worldwide as a standard treatment.[4,9,11] In the present study, methotrexate still maintained a high rate of use despite its declining trend.

This study has some unavoidable limitations. First, the study drugs include those that may be used outside of treatment for JIA. For example, drugs with multiple indications such as glucocorticoids and NSAIDs. The present study could not completely rule out these inclusions. Second, the disease names are for reimbursement claims, and there was no verification that the coding accurately reflected medically based disease names. Therefore, misclassification of JIA disease types may not have been completely eliminated. Third, the database used in this study includes working-age individuals and their dependents. If a parent changes insurers due to transfer or other reasons, the insurance of their dependents, the patients in this study, will also change and may not be traceable. Fourth, the subjects of this study did not include relatively mild JIA patients who did not use bDMARDs. This study shows the trend of drugs used in relatively severe JIA patients who use bDMARDs. Nevertheless, we believe that our findings reflect the actual clinical practice of moderate-to-severe JIA treatment in Japan, since this is a nationwide database study. In addition, although there are a limited number of patients aged ≥65 years in this database, this fact does not limit our study because the patients in this study were younger than 16 years old.

In conclusion, we investigated the use of bDMARDs in patients with moderate-to-severe JIA using a large nationwide database in Japan. Consistent with our previously reported results in RA,[10] we found an increasing trend for adalimumab and tocilizumab and a decreasing trend for methotrexate. The different use of drugs in patients with sJIA and non-sJIA was also evident, which is consistent with national and international guidelines. The introduction of bDMARDs has markedly improved the efficacy of JIA treatment.[30,33] In addition, more patients can now avoid the safety concerns associated with conventional methotrexate and glucocorticoids, but there are still many issues to be examined regarding the short- and long-term safety of bDMARDs, including the risk of infection and potential risk of malignancy associated with their immunosuppressive effects. Future studies are needed to clarify these issues.

Data Sharing Statement

The data that support the findings of this study are available from JMDC Inc. but were used under license for the current study; therefore, restrictions apply and the data are not publicly available. For inquiries about access to the dataset used in this study, please contact JMDC (https://www.jmdc.co.jp).

Ethics Approval

All procedures in this study involving human participants were performed in accordance with the ethical standards of the institutional research committee, and with the 1964 Declaration of Helsinki, its later amendments and comparable ethical standards. This study was approved by the Ethics Committee of Osaka Medical and Pharmaceutical University (Approval ID: 2762-1) on August 6, 2019.

Consent to Participate

This study used anonymised information from the "JMDC Claims Database"; therefore, in accordance with the ethical guidelines for medical and health research involving human subjects in Japan, informed consent was not required.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

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

Disclosure

Professor Masashi Neo reports personal fees from DePuy Synthes Products, outside the submitted work. The authors declare that there are no other conflicts of interest.

References

1. Petty RE, Southwood TR, Manners P, et al. International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. *J Rheumatol*. 2004;31(2):390–392.
2. Yokota S, Mori M, Imagawa T, et al. Proposal for juvenile idiopathic arthritis guidance on diagnosis and treatment for primary care pediatricians and nonpediatric rheumatologists (2007). *Mod Rheumatol*. 2007;17(5):353–363. doi:10.3109/s10165-007-0625-4
3. Fink CW. Proposal for the development of classification criteria for idiopathic arthritides of childhood. *J Rheumatol*. 1995;22(8):1566–1569.
4. Okamoto N, Yokota S, Takei S, et al. Clinical practice guidance for juvenile idiopathic arthritis (JIA) 2018. *Mod Rheumatol*. 2019;29(1):41–59. doi:10.1080/14397595.2018.1514724
5. Akioka S. Interleukin-6 in juvenile idiopathic arthritis. *Mod Rheumatol*. 2019;29(2):275–286. doi:10.1080/14397595.2019.1574697
6. Rose-John S, Scheller J, Elson G, Jones SA. Interleukin-6 biology is coordinated by membrane-bound and soluble receptors: role in inflammation and cancer. *J Leukoc Biol*. 2006;80(2):227–236. doi:10.1189/jlb.1105674
7. Fung A, Yue X, Wigle PR, Guo JJ. Off-label medication use in rare pediatric diseases in the United States. *Intractable Rare Dis Res*. 2021;10(4):238–245. doi:10.5582/irdr.2021.01104
8. Eisenstein EM, Berkun Y. Diagnosis and classification of juvenile idiopathic arthritis. *J Autoimmun*. 2014;48–49:31–33. doi:10.1016/j.jaut.2014.01.009
9. Onel K, Rumsey DG, Shenoi S. Juvenile idiopathic arthritis treatment updates. *Rheum Dis Clin North Am*. 2021;47(4):545–563. doi:10.1016/j.rdc.2021.07.009
10. Hirata A, Ota R, Hata T, et al. Prescribing trends of biologic disease-modifying anti-rheumatic drugs using a claims database from 6 million people in Japan. *Clin Drug Investig*. 2021;41(11):967–974. doi:10.1007/s40261-021-01082-x
11. Onel KB, Horton DB, Lovell DJ, et al. 2021 American college of rheumatology guideline for the treatment of juvenile idiopathic arthritis: therapeutic approaches for oligoarthritis, temporomandibular joint arthritis, and systemic juvenile idiopathic arthritis. *Arthritis Care Res*. 2022;74(4):521–537. doi:10.1002/acr.24853
12. Beukelman T, Ringold S, Davis TE, et al. Disease-modifying antirheumatic drug use in the treatment of juvenile idiopathic arthritis: a cross-sectional analysis of the CARRA registry. *J Rheumatol*. 2012;39(9):1867–1874. doi:10.3899/jrheum.120110
13. Anink J, Otten MH, Gorter SL, et al. Treatment choices of paediatric rheumatologists for juvenile idiopathic arthritis: etanercept or Adalimumab? *Rheumatology*. 2013;52(9):1674–1679. doi:10.1093/rheumatology/ket170
14. Stoll ML, Cron RQ. Treatment of juvenile idiopathic arthritis: a revolution in care. *Pediatr Rheumatol Online J*. 2014;12(1):13. doi:10.1186/1546-0096-12-13
15. Ringold S, Angeles-Han ST, Beukelman T, et al. 2019 American college of rheumatology/Arthritis foundation guideline for the treatment of juvenile idiopathic arthritis: therapeutic approaches for non-systemic polyarthritis, sacroiliitis, and enthesitis. *Arthritis Care Res*. 2019;71(6):717–734. doi:10.1002/acr.23870
16. Yue X, Huang B, Hincapie AL, et al. Comparative effectiveness and persistence of TNFi and non-TNFi in juvenile idiopathic arthritis: a large paediatric rheumatology centre in the USA. *Rheumatology*. 2021;60(9):4063–4073. doi:10.1093/rheumatology/keaa877
17. Woerner A, Uettwiller F, Melki I, et al. Biological treatment in systemic juvenile idiopathic arthritis: achievement of inactive disease or clinical remission on a first, second or third biological agent. *RMD Open*. 2015;1(1):e000036. doi:10.1136/rmdopen-2014-000036
18. Horneff G, Klein A, Klotsche J, et al. Comparison of treatment response, remission rate and drug adherence in polyarticular juvenile idiopathic arthritis patients treated with etanercept, Adalimumab or tocilizumab. *Arthritis Res Ther*. 2016;18(1):272. doi:10.1186/s13075-016-1170-3
19. Patil P, Parker RA, Rawcliffe C, et al. Methotrexate-induced nausea and vomiting in adolescent and young adult patients. *Clin Rheumatol*. 2014;33(3):403–407. doi:10.1007/s10067-013-2389-x
20. Kearsley-Fleet L, Vicente González L, Steinke D, et al. Methotrexate persistence and adverse drug reactions in patients with juvenile idiopathic arthritis. *Rheumatology*. 2019;58(8):1453–1458. doi:10.1093/rheumatology/kez048
21. Yue X, Huang B, Hincapie AL, et al. Prescribing patterns and impact of factors associated with time to initial biologic therapy among children with non-systemic juvenile idiopathic arthritis. *Paediatr Drugs*. 2021;23(2):171–182. doi:10.1007/s40272-021-00436-4
22. Ruperto N, Brunner HI, Pacheco-Tena C, et al. Open-label Phase 3 study of intravenous golimumab in patients with polyarticular juvenile idiopathic arthritis. *Rheumatology*. 2021;60(10):4495–4507. doi:10.1093/rheumatology/keab021
23. Brunner HI, Ruperto N, Tzaribachev N, et al. Subcutaneous golimumab for children with active polyarticular-course juvenile idiopathic arthritis: results of a multicentre, double-blind, randomised-withdrawal trial. *Ann Rheum Dis*. 2018;77(1):21–29. doi:10.1136/annrheumdis-2016-210456
24. Lanz S, Seidel G, Skrabl-Baumgartner A. Golimumab in juvenile idiopathic arthritis-associated uveitis unresponsive to Adalimumab. *Pediatr Rheumatol Online J*. 2021;19(1):132. doi:10.1186/s12969-021-00630-1
25. Ruperto N, Lovell DJ, Cuttica R, et al. A randomized, placebo-controlled trial of infliximab plus methotrexate for the treatment of polyarticular-course juvenile rheumatoid arthritis. *Arthritis Rheum*. 2007;56(9):3096–3106. doi:10.1002/art.22838
26. Lahdenne P, Vähäsalo P, Honkanen V. Infliximab or etanercept in the treatment of children with refractory juvenile idiopathic arthritis: an open label study. *Ann Rheum Dis*. 2003;62(3):245–247. doi:10.1136/ard.62.3.245
27. Visvanathan S, Wagner C, Marini JC, et al. The effect of infliximab plus methotrexate on the modulation of inflammatory disease markers in juvenile idiopathic arthritis: analyses from a randomized, placebo-controlled trial. *Pediatr Rheumatol Online J*. 2010;8(1):24. doi:10.1186/1546-0096-8-24
28. Tynjälä P, Lindahl P, Honkanen V, Lahdenne P, Kotaniemi K. Infliximab and etanercept in the treatment of chronic uveitis associated with refractory juvenile idiopathic arthritis. *Ann Rheum Dis*. 2007;66(4):548–550. doi:10.1136/ard.2006.058248
29. Cecchin V, Zannin ME, Ferrari D, et al. Longterm safety and efficacy of adalimumab and infliximab for uveitis associated with juvenile idiopathic arthritis. *J Rheumatol*. 2018;45(8):1167–1172. doi:10.3899/jrheum.171006
30. Batu ED. Glucocorticoid treatment in juvenile idiopathic arthritis. *Rheumatol Int*. 2019;39(1):13–27. doi:10.1007/s00296-018-4168-0
31. Minoia F, Davì S, Horne A, et al. Clinical features, treatment, and outcome of macrophage activation syndrome complicating systemic juvenile idiopathic arthritis: a multinational, multicenter study of 362 patients. *Arthritis Rheumatol*. 2014;66(11):3160–3169. doi:10.1002/art.38802
32. Sönmez HE, Demir S, Bilginer Y, Özen S. Anakinra treatment in macrophage activation syndrome: a single center experience and systemic review of literature. *Clin Rheumatol*. 2018;37(12):3329–3335. doi:10.1007/s10067-018-4095-1
33. Golhen K, Winskill C, Yeh C, Zhang N, Welzel T, Pfister M. Value of literature review to inform development and use of biologics in juvenile idiopathic arthritis. *Front Pediatr*. 2022;10:909118. doi:10.3389/fped.2022.909118