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Safety and effectiveness of intravenous abatacept for polyarticular-course juvenile idiopathic arthritis: An all-case postmarketing surveillance study

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Abstract

Background In 2018, intravenous abatacept was approved for the treatment of refractory polyarticular-course juvenile idiopathic arthritis (JIA) in Japan. However, reports describing the effectiveness and safety of abatacept in clinical practice in Japanese patients with refractory polyarticular-course JIA are limited. Therefore, this postmarketing surveillance study aimed to evaluate the real-world safety and effectiveness of abatacept in Japanese pediatric patients with refractory polyarticular-course JIA.

Methods This study evaluated patients included in an all-case postmarketing surveillance study between February 2018 and August 2020 who were treated with intravenous abatacept. Data on the safety and effectiveness of the registered patients were collected during the 52-week follow-up period. Disease activities were evaluated using Juvenile Arthritis Disease Activity Score 27 (JADAS-27). The effect of abatacept on a child's growth was assessed using the height and weight standard deviation scores (SDS).

Results A total of 82 patients were registered in this study, of whom 14.6% and 85.4% were males and females, respectively. The proportion of patients with oligoarticular, rheumatoid factor (RF)-negative polyarticular, and RF-positive polyarticular JIA was 12.2, 28.0, and 54.9%, respectively. The incidence of adverse drug reactions (ADRs) and serious ADRs was 22.0% and 2.4%, respectively. During the study period, 64.7% of the patients achieved JADAS-27 low disease activity or less. A significant difference in JADAS-27 scores in patients with RF-positive polyarticular JIA was observed between baseline and 24 or 52 weeks after abatacept administration. The height and weight SDS tended to improve during abatacept treatment.

Conclusions Abatacept is effective in polyarticular-course JIA, particularly in RF-positive patients, and in restoring a child's growth. Additionally, the incidence of ADRs is similar to that observed in the clinical trial. The results of the study suggest that abatacept is a useful therapeutic option for treating refractory polyarticular-course JIA in real-world settings in Japan.

Keywords Polyarticular-course juvenile idiopathic arthritis, Abatacept, Postmarketing surveillance study, Juvenile Arthritis Disease Activity Score 27, Standard deviation score, Growth retardation

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Background

Juvenile idiopathic arthritis (JIA) is a pediatric rheumatic disease of unknown etiology that occurs in children aged < 16 years [1]. Methotrexate (MTX) is used as a first-line treatment for JIA in Japan [2]. However, if disease activity remains moderate or high 3 months after initiating MTX treatment, second-line treatment should be initiated with biologic disease-modifying anti-rheumatic drugs (bDMARDs), such as tumor necrosis factor-α (TNF-α) inhibitors or interleukin (IL)−6 receptor blockers [3, 4]. The TNF-α inhibitors etanercept and adalimumab and the IL-6 receptor blocker tocilizumab were approved for treating polyarticular-course JIA in Japan before abatacept was approved.

Intravenous abatacept was approved in Japan for the treatment of refractory polyarticular-course JIA in 2018. Abatacept is a fusion protein that contains an extracellular domain of human cytotoxic T-lymphocyte-associated protein 4 and an Fc portion of human immunoglobulin G1. Additionally, abatacept selectively inhibits T cell activation by binding to CD80/86 and modulating its interaction with CD28 [5]. A phase III open-label study investigated the efficacy and safety of abatacept in Japanese patients with polyarticular-course JIA [6]. The results showed that abatacept was efficacious and well-tolerated in these patients. However, reports describing the effectiveness and safety of abatacept in clinical practice in Japanese patients with refractory polyarticular-course JIA are limited.

Therefore, this postmarketing surveillance (PMS) study aimed to evaluate the real-world safety and effectiveness of abatacept in Japanese patients with refractory polyarticular-course JIA.

Methods

Study design and patients

This all-case PMS study targeted patients with polyarticular-course JIA. All patients who were treated with abatacept in Japanese medical institutions between February 2018 and August 2020 were included in the study. Data on the safety and effectiveness of abatacept in the registered patients were collected during the 52-week follow-up period. All patients with polyarticular-course JIA who had received commercial abatacept in Japan after the drug approval were included in this PMS study. The polyarticular-course JIA for which abatacept is indicated includes extended oligoarticular, rheumatoid factor (RF)-positive polyarticular, RF-negative polyarticular, enthesitis-related, psoriatic, undifferentiated, and systemic (when systemic symptoms are stable and polyarthritis is the main symptom) JIA, which indicates that abatacept could be applicable to all diseases classified under the seven categories of the International League of Associations for Rheumatology (ILAR). In this study, the investigator determined whether a patient with oligoarthritis progressed to polyarthritis. The investigator also assessed whether the patient's condition was refractory to any existing treatments. Abatacept was administered as an intravenous infusion (after the initial dose, it was administered at weeks 2 and 4 and every 4 weeks subsequently). The recommended abatacept dose was based on the patient's body weight as follows: < 75 kg, 10 mg/kg; 75–100 kg, 750 mg; and > 100 kg, 1000 mg. This was in accordance with the indications listed in the package insert for the appropriate use of abatacept. The collected data included age, sex, pregnancy/breastfeeding, age, weight, reasons for treatment with abatacept, ILAR classification at diagnosis, duration of disease, medical history, comorbidities, prior use of bDMARDs, glucocorticoids, and MTX, and MTX dose at the start of abatacept administration.

Endpoints and assessments

Data on adverse events (defined as any undesirable experience observed during the use of abatacept in a patient), adverse drug reactions (ADRs) (defined as any adverse events for which a causal relationship with the use of the drug could not be ruled out), and serious ADRs (defined as any ADRs causing death, life-threatening, hospitalization or prolongation of existing hospitalization, persistent or significant disability/incapacity, congenital anomaly/birth defect, and other medically important conditions) that occurred during the observation period were prospectively collected. ADRs were reported using MedDRA (v. 24.0; Maintenance and Support Services Organization, McLean, VA, USA). Disease activities were evaluated using Juvenile Arthritis Disease Activity Score 27 (JADAS-27 [erythrocyte sedimentation rate]) before and at weeks 24 and 52 of abatacept treatment. The JADAS-27 is divided into four categories based on the cut-off values for polyarthritis and oligoarthritis as follows: inactive disease (both ≤ 1), low disease activity (1.1–3.8 and 1.1–2, respectively), moderate disease activity (3.9–8.5 and 2.1–4.2, respectively), and high disease activity (> 8.5 and > 4.2, respectively) [7]. Additionally, the time course of matrix metalloproteinase-3 (MMP-3) levels was evaluated, and the responders for abatacept were defined as patients with 2.0 or less in JADAS-27 (C-reactive protein) at 52 weeks after abatacept administration with data imputation using the last observation carried forward (LOCF) method. The effect of abatacept on growth was evaluated using the height and weight standard deviation (SD) scores (SDS).

Statistical analyses

Continuous variables were reported as mean, SD, minimum, and maximum. Categorical variables were summarized as the number and proportion of the overall patients and subgroups. Data from all patients who received at least one dose of abatacept were included in the safety evaluation. The probability of continuation of oral corticosteroids or MTX over time was estimated using the Kaplan–Meier method. ADRs were summarized by system organ class (SOC) and preferred term (PT). Effectiveness was evaluated in all patients for whom JADAS-27 was available before and after abatacept treatment, and the LOCF method was used to impute data for withdrawals. For JADAS-27 scores, a paired t-test was used to compare between baseline and 24 or 52 weeks. Regarding changes from baseline in height and weight SDS, a 95% confidence interval was calculated. All statistical analyses were performed using SAS V. 9.3 (SAS Institute Inc., Cary, NC, USA).

Results

Patient disposition and baseline characteristics

A total of 82 patients, with a mean (SD) age of 14.0 (6.8) years, were included in this study, among whom 14.6% (12 of 82) were male and 85.4% (70 of 82) were female. Overall, 82 and 81 patients were included in the safety and effectiveness analysis sets, respectively. Of the 82 patients in the safety analysis set, 17 had been receiving abatacept for over a 1 year from the phase III clinical trial [6] when this study began (continuously treated patients), while 65 received abatacept for the first time in this study (newly treated patients). Among the 81 patients included in the effectiveness analysis set, 16 and 65 were continuously and newly treated patients, respectively (Figure 1).

Ten (12.2%) patients had oligoarticular, 23 (28.0%) had RF-negative polyarticular, 45 (54.9%) had RF-positive polyarticular, and 4 (4.9%) had other JIA. The proportion of patients with a history of prior treatment with bDMARDs, corticosteroids, and MTX was 69.5% (57 of 82), 69.5% (57 of 82), and 95.1% (78 of 82), respectively (Table 1).

The laboratory test data (RF, anti-citrullinated protein antibody [ACPA], MMP-3, and antinuclear antibody levels) at the start of drug administration in the safety analysis set are shown in Additional file 1. Furthermore, the proportion of patients with negative/positive ACPA according to the ILAR classification is presented in Additional file 2.

Status of abatacept administration and oral corticosteroid and MTX use

During the study period, 20 of the 82 patients (24.4%) discontinued treatment with abatacept. Of these, 13 patients had an insufficient response, and 3 discontinued treatments because of adverse events (Table 2).

At the start of the study, 43.9% (36 of 82) of patients were taking concomitant oral corticosteroids. During the study period, 16.7% (6 of 36) and 38.9% (14 of 36) of patients reduced or discontinued oral corticosteroid doses, respectively. Among the patients who discontinued oral corticosteroids, none discontinued treatment because of adverse events (Table 3). Figure 2a

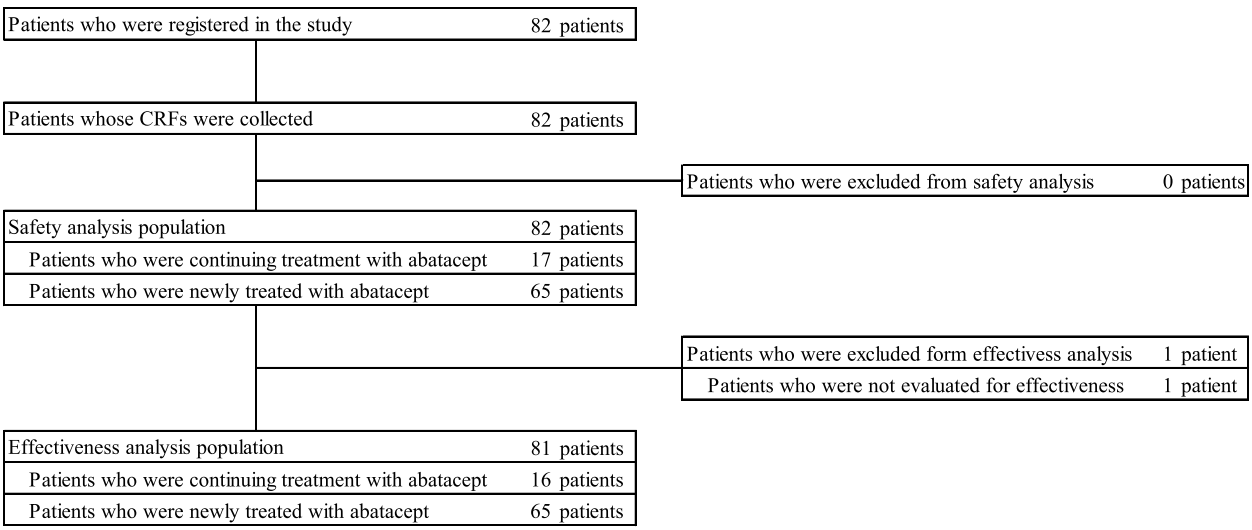


Fig. 1 Patient disposition. The flow chart shows the selection of patients for this study. A total of 82 patients were included in this study. Of the 82 patients in the safety analysis set, 17 continued treatment with abatacept from the clinical trial, and 65 were newly treated with abatacept. Among the 81 patients included in the effectiveness analysis set, 16 were continuing treatment with abatacept, and 65 were newly treated with abatacept

Table 1 Baseline patient characteristics

		Safety analysis population					
		Overall (%)		**Continuously treated patients (%)**		**Newly treated patients (%)**	
		***n*=82**		***n*=17**		***n*=65**	
Sex	Male	12	(14.6)	3	(17.6)	9	(13.8)
	Female	70	(85.4)	14	(82.4)	56	(86.2)
Pregnancy/Breastfeeding (for women)	Not pregnant/Not breastfeeding	70	(100.0)	14	(100.0)	56	(100.0)
	Not specified	0	(0.0)	0	(0.0)	0	(0.0)
Age (year)	Mean (SD)	14.0 (6.8)		15.6 (6.1)		13.5 (6.9)	
	Minimum, Maximum	2, 52		8, 36		2, 52	
Height (cm)	Mean (SD)	144.9 (18.4)		153.4 (10.4)		142.6 (19.4)	
	Minimum, Maximum	86.3, 174.0		132.0, 174.0		86.3, 164.8	
Weight (kg)	Mean (SD)	41.1 (13.6)		47.2 (11.3)		39.5 (13.7)	
	Minimum, Maximum	11.4, 74.0		29.6, 74.0		11.4, 67.0	
Reasons for treatment with abatacept	Active polyarticular juvenile idiopathic arthritis with insufficient effectiveness of existing treatments	82	(100.0)	17	(100.0)	65	(100.0)
	Others	0	(0.0)	0	(0.0)	0	(0.0)
ILAR classification at diagnosis	Systemic	2	(2.4)	0	(0.0)	2	(3.1)
	Oligoarticular	10	(12.2)	1	(5.9)	9	(13.8)
	RF-negative polyarticular	23	(28.0)	6	(35.3)	17	(26.2)
	RF-positive polyarticular	45	(54.9)	9	(52.9)	36	(55.4)
	Psoriatic	0	(0.0)	0	(0.0)	0	(0.0)
	Enthesitis-related	2	(2.4)	1	(5.9)	1	(1.5)
	Undifferentiated	0	(0.0)	0	(0.0)	0	(0.0)
	Unknown	0	(0.0)	0	(0.0)	0	(0.0)
Duration of disease (year)	Mean (SD)	5.43 (6.13)		6.41 (4.13)		5.19 (6.54)	
	Minimum, Maximum	0.3, 42.2		2.6, 20.8		0.3, 42.2	
Medical history	No	66	(80.5)	16	(94.1)	50	(76.9)
	Yes	16	(19.5)	1	(5.9)	15	(23.1)
Comorbidity	No	32	(39.0)	4	(23.5)	28	(43.1)
	Yes	50	(61.0)	13	(76.5)	37	(56.9)
History of prior treatment with bDMARD	No	25	(30.5)	0	(0.0)	25	(38.5)
	Yes	57	(69.5)	17	(100.0)	40	(61.5)
	Tocilizumab	32	(39.0)	4	(23.5)	28	(43.1)
	Etanercept	16	(19.5)	3	(17.6)	13	(20.0)
	Adalimumab	27	(32.9)	4	(23.5)	23	(35.4)
	Others	22	(26.8)	17	(100.0)	5	(7.7)
	Unknown	0	(0.0)	0	(0.0)	0	(0.0)
History of prior treatment with corticosteroids	No	25	(30.5)	7	(41.2)	18	(27.7)
	Yes	57	(69.5)	10	(58.8)	47	(72.3)
History of prior treatment with MTX	No	4	(4.9)	0	(0.0)	4	(6.2)
	Yes	78	(95.1)	17	(100.0)	61	(93.8)
	Unknown	0	(0.0)	0	(0.0)	0	(0.0)
MTX dose at the initiation of abatacept administration (mg/m^2/week)	N	55		-		-	
	Mean (SD)	8.0 (2.2)		-		-	
	Minimum, Maximum	3.8, 14.2		-		-	

SD standard deviation, *ILAR* International League of Associations for Rheumatology, *RF* rheumatoid factor, *bDMARD* biologic disease-modifying anti-rheumatic drugs, *MTX* methotrexate

Table 2 Status of abatacept administration

Duration of treatment with abatacept	Patients who discontinued treatment with abatacept		Reasons for discontinuation					
	n	%	Occurrence of adverse events	Remission	Insufficient	Loss to follow-up	Transfer to other hospitals	Other
< 12 weeks	8	9.8	1	0	7	1	0	0
≥ 12 weeks, < 24 weeks	3	3.7	2	0	1	1	0	1
≥ 24 weeks, < 36 weeks	4	4.9	0	0	4	0	0	0
≥ 36 weeks, < 48 weeks	5	6.1	0	0	1	0	2	2
≥ 48 weeks, < 52 weeks	0	0.0	0	0	0	0	0	0
Total	20	24.4	3	0	13	2	2	3

Table 3 Status of oral corticosteroid use

		Number of patients (%)	
Safety analysis population		**82**	
Concomitant use of oral corticosteroids			
No		**46**	**(56.1)**
Yes*		36	(43.9)
	Oral corticosteroids were used at the start of treatment with abatacept	36	(100.0)
	Oral corticosteroids were not discontinued during treatment with abatacept	21	(58.3)
	Oral corticosteroid doses were ultimately increased during treatment with abatacept	4	(11.1)
	Oral corticosteroid doses were not changed during treatment with abatacept	11	(30.6)
	Oral corticosteroid doses were ultimately reduced during treatment with abatacept	6	(16.7)
	Oral corticosteroids were discontinued during treatment with abatacept	14	(38.9)
	Oral corticosteroids were discontinued due to an adverse event	0	(0.0)
	Unknown whether oral corticosteroids were discontinued during the treatment period	1	(2.8)
	Treatment with oral corticosteroids was started during treatment with abatacept	0	(0.0)

* The percentages of breakdown categories are calculated based on the number of patients with concomitant use of oral corticosteroids

shows the probability of continuation of oral corticosteroids by the Kaplan–Meier method. The mean (SD) body weight-adjusted doses of oral corticosteroids at the start and end of treatment with abatacept were 0.20 (0.14) and 0.11 (0.16) mg/kg/day, respectively (Figure 2b).

At the start of the study, 68.3% (56 of 82) of the patients were concomitantly taking MTX (Table 4). The mean (SD) dose of MTX was 8.0 (2.2) mg/m^2/week at the start of abatacept administration (Table 1). During the study period, 16.1% (9 of 56) and 16.1% (9 of 56) of patients had their MTX dose reduced or discontinued, respectively. Of the nine patients who discontinued MTX, four discontinued it because of adverse events (Table 4). The probability of continuation of MTX by the Kaplan–Meier method is shown in Additional file 3.

Safety

Incidence of ADRs and serious ADRs and timing of ADR onset in newly treated patients

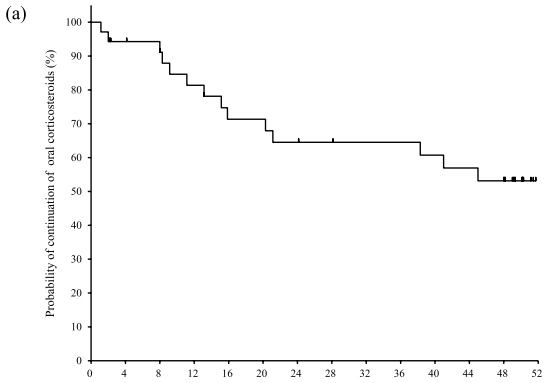
The incidence of ADRs was 22.0% (18 of 82) (Table 5), whereas that of serious ADRs was 2.4% (2 of 82) (Table 6).

Specifically, the timing of the onset of ADRs in patients in whom abatacept was newly administered is shown by the SOC and PT in Additional file 4. The proportion of patients who experienced ADRs was 18.5% (12 of 65) at < 24 weeks and 6.2% (4 of 65) at ≥ 24 weeks after the start of abatacept administration.

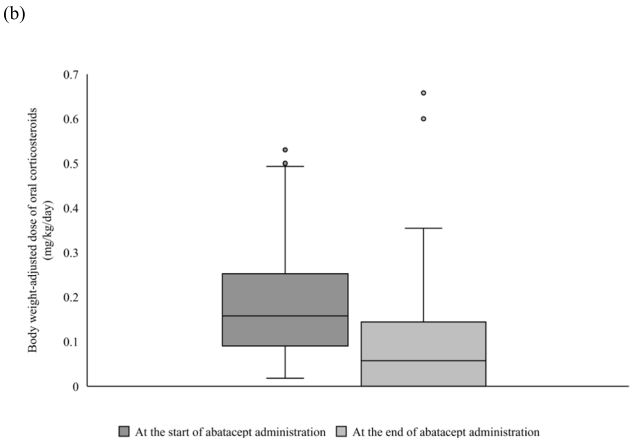
Effectiveness

JADAS-27 evaluation

The mean (SD) JADAS-27 scores in the overall and newly treated patients were 10.2 (9.6) and 12.5 (9.8) at baseline, 5.5 (7.2) and 6.1 (7.2) at 24 weeks, and 4.9 (7.2) and 5.5



Week	At risk	No. of patients discontinued oral corticosteroids	Probability of continuation of oral corticosteroids (%)	95% CI
0	35	-	-	-
4	31	2	94.29	(79.03, 98.54)
8	30	3	91.14	(74.95, 97.06)
12	25	6	81.38	(63.07, 91.20)
16	21	9	71.33	(51.99, 83.99)
20	21	9	71.33	(51.99, 83.99)
24	19	11	64.54	(45.02, 78.64)
28	18	11	64.54	(45.02, 78.64)
32	17	11	64.54	(45.02, 78.64)
36	17	11	64.54	(45.02, 78.64)
40	16	12	60.74	(41.10, 75.61)
44	15	13	56.94	(37.34, 72.48)
48	14	14	53.15	(33.72, 69.25)
52	-	-	-	(- , -)



	At the start of abatacept administration	At the end of abatacept administration
N	34	34
Mean (SD)	0.20 (0.14)	0.11 (0.16)
Minimum, Maximum	0.02, 0.53	0.00, 0.66

Fig. 2 Probability of continuation of oral corticosteroids and change in the dose of oral corticosteroids. The probability of continuation of oral corticosteroids from the start of abatacept administration (**a**) and the body weight-adjusted dose of oral corticosteroids at the start and end of abatacept administration (**b**) are shown. CI, confidence interval; SD, standard deviation

Table 4 Status of methotrexate use

		Number of patients (%)	
Safety analysis population		82	
Concomitant use of MTX			
No		26	(31.7)
Yes[a]		56	(68.3)
	MTX was used at the start of treatment with abatacept	56	(100.0)
	MTX was not discontinued during treatment with abatacept	46	(82.1)
	MTX dose was ultimately increased during treatment with abatacept	2	(3.6)
	MTX dose was not changed during treatment with abatacept	35	(62.5)
	MTX dose was ultimately reduced during treatment with abatacept	9	(16.1)
	MTX was discontinued during treatment with abatacept	9	(16.1)
	MTX was discontinued due to an adverse event	4	(7.1)
	Unknown whether MTX was discontinued during the treatment period	1	(1.8)
	Treatment with MTX was started during treatment with abatacept	0	(0.0)

[a] The percentages of breakdown categories are calculated based on the number of patients with concomitant use of MTX

MTX methotrexate

(7.3) at 52 weeks after abatacept administration, respectively. In both the overall and newly treated patients, significant differences in JADAS-27 scores were observed between baseline and 24 or 52 weeks after abatacept administration (Figures 3a and 3b). At 52 weeks after abatacept administration, 64.7% of the overall patients achieved JADAS-27 low disease activity or inactive disease, whereas 23.5% still had high disease activity. This trend was similar when limited to the newly treated patients (low disease activity or inactive disease, 59.4%; high disease activity, 27.0%). The proportion of patients with high disease activity status based on JADAS-27 decreased over time in the overall and newly treated patients (Figures 3c and 3d).

Table 5 Incidence of adverse drug reactions

Adverse drug reactions*		Safety analysis population					
		Overall (%) *n* = 82		Continuously treated patients (%) *n* = 17		Newly treated patients (%) *n* = 65	
Number of patients who experienced adverse drug reactions (%)		18	(22.0)	4	(23.5)	14	(21.5)
Number of adverse drug reactions		28		4		24	
Infections and infestations		7	(8.5)	2	(11.8)	5	(7.7)
	Acute sinusitis	1	(1.2)	0	(0.0)	1	(1.5)
	Bronchitis	2	(2.4)	0	(0.0)	2	(3.1)
	Gastroenteritis	1	(1.2)	0	(0.0)	1	(1.5)
	Herpes simplex	1	(1.2)	1	(5.9)	0	(0.0)
	Influenza	1	(1.2)	0	(0.0)	1	(1.5)
	Nasopharyngitis	1	(1.2)	1	(5.9)	0	(0.0)
	Otitis media acute	1	(1.2)	0	(0.0)	1	(1.5)
	Pneumonia	1	(1.2)	0	(0.0)	1	(1.5)
	Subcutaneous abscess	1	(1.2)	0	(0.0)	1	(1.5)
	Varicella	1	(1.2)	0	(0.0)	1	(1.5)
	Fungal esophagitis	1	(1.2)	0	(0.0)	1	(1.5)
Immune system disorders		1	(1.2)	0	(0.0)	1	(1.5)
	Hypersensitivity	1	(1.2)	0	(0.0)	1	(1.5)
Eye disorders		1	(1.2)	1	(5.9)	0	(0.0)
	Chalazion	1	(1.2)	1	(5.9)	0	(0.0)
Ear and labyrinth disorders		1	(1.2)	0	(0.0)	1	(1.5)
	Ear discomfort	1	(1.2)	0	(0.0)	1	(1.5)
Respiratory, thoracic, and mediastinal disorders		2	(2.4)	0	(0.0)	2	(3.1)
	Upper respiratory tract inflammation	2	(2.4)	0	(0.0)	2	(3.1)
Gastrointestinal disorders		4	(4.9)	0	(0.0)	4	(6.2)
	Abdominal pain	1	(1.2)	0	(0.0)	1	(1.5)
	Stomatitis	3	(3.7)	0	(0.0)	3	(4.6)
Skin and subcutaneous tissue disorders		1	(1.2)	0	(0.0)	1	(1.5)
	Dry skin	1	(1.2)	0	(0.0)	1	(1.5)
	Erythema	1	(1.2)	0	(0.0)	1	(1.5)
	Perioral dermatitis	1	(1.2)	0	(0.0)	1	(1.5)
Musculoskeletal and connective tissue disorders		1	(1.2)	1	(5.9)	0	(0.0)
	Arthritis	1	(1.2)	1	(5.9)	0	(0.0)
Investigations		3	(3.7)	0	(0.0)	3	(4.6)
	Transaminases increased	1	(1.2)	0	(0.0)	1	(1.5)
	Hepatic enzyme increased	1	(1.2)	0	(0.0)	1	(1.5)
	Matrix metalloproteinase-3 increased	1	(1.2)	0	(0.0)	1	(1.5)

* Adverse drug reactions were coded using MedDRA version 24.0

Furthermore, the time course in JADAS-27, according to the ILAR classification, decreased over time for oligoarticular, RF-negative polyarticular, and RF-positive polyarticular JIA (Figures 4a–4c). A significant difference was observed in JADAS-27 scores in patients with RF-positive polyarticular JIA between baseline and 24 or 52 weeks after abatacept administration (Figure 4c). The proportion of patients with high disease activity status based on JADAS-27 decreased over time for each disease. Specifically, the proportion of patients with high disease activity at baseline and 52 weeks after abatacept administration were 100.0% and 25.0% in patients with oligoarticular JIA, 37.5% and 25.0% in those with RF-negative polyarticular JIA, and 42.9% and 17.9% in those with RF-positive polyarticular JIA, respectively (Figures 4d–4f). Based on the trends and changes in JADAS-27 among patients with

Table 6 Incidence of serious adverse drug reactions

Serious adverse drug reactions*		Safety analysis population					
		Overall (%) *n* = 82		Continuously treated patients (%) *n* = 17		Newly treated patients (%) *n* = 65	
Number of patients who experienced serious adverse drug reactions (%)		2	(2.4)	0	(0.0)	2	(3.1)
Number of serious adverse drug reactions		3		0		3	
Infections and infestations		2	(2.4)	0	(0.0)	2	(3.1)
	Bronchitis	1	(1.2)	0	(0.0)	1	(1.5)
	Pneumonia	1	(1.2)	0	(0.0)	1	(1.5)
	Varicella	1	(1.2)	0	(0.0)	1	(1.5)

* Serious adverse drug reactions were coded using MedDRA version 24.0

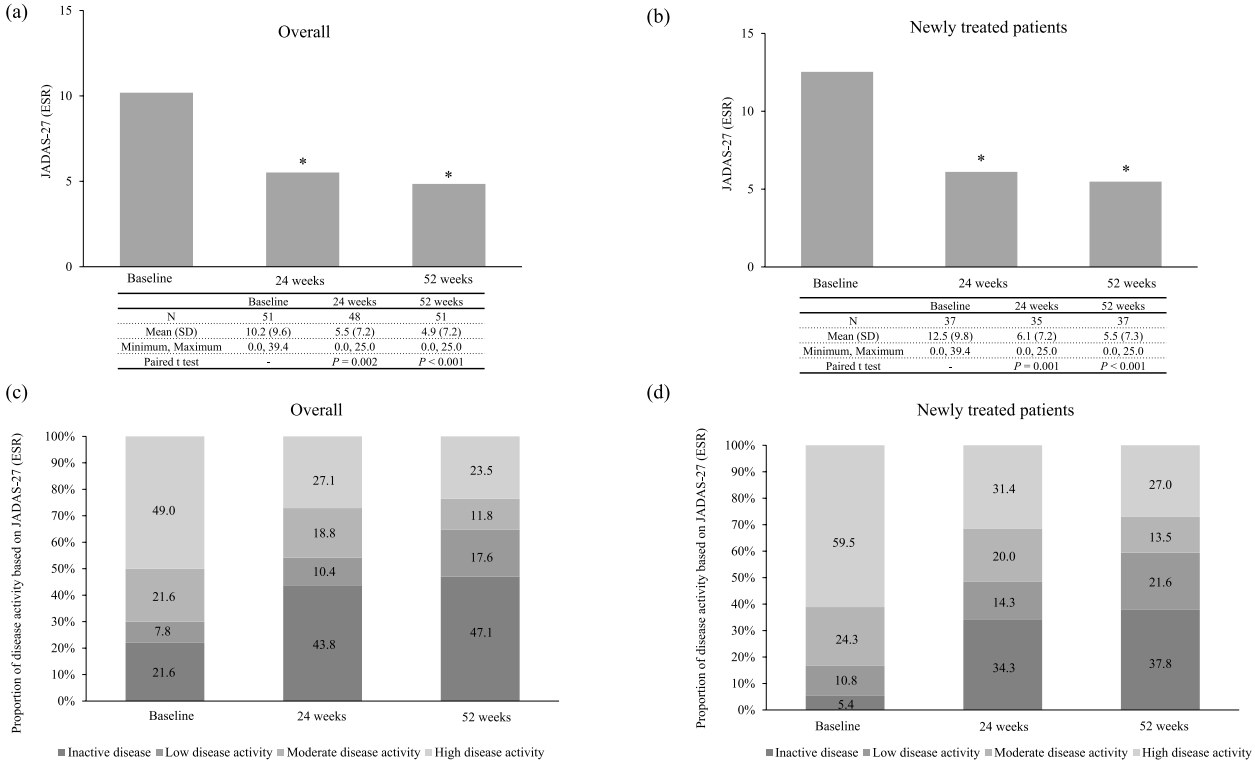
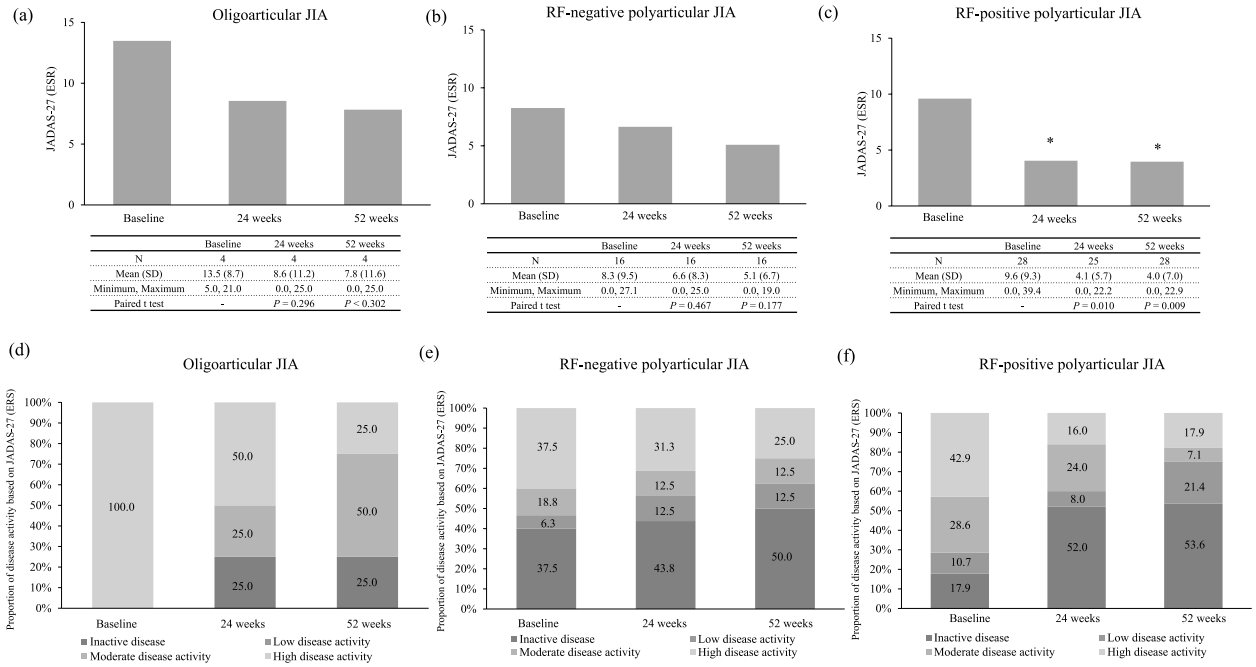


Fig. 3 Time course of JADAS-27 scores and disease activity status. The mean (SD) JADAS-27 scores over time in overall patients (**a**) and patients who were newly treated with abatacept (**b**) are shown. The disease activity status based on JADAS-27 over time in overall patients (**c**) and patients who were newly treated with abatacept (**d**) are shown. A paired t-test was used for statistical analysis, with $P < 0.05$ considered to indicate statistical significance. An asterisk (*) indicates a significant difference was found when compared with baseline. JADAS, Juvenile Arthritis Disease Activity Score; ESR, erythrocyte sedimentation rate

RF- and ACPA-negative/positive polyarthritis, improvement was observed in those with RF-positive polyarthritis and ACPA-positive disease pathology (Additional file 5).

The mean (SD) JADAS-27 at baseline, 24 weeks, and 52 weeks were 15.0 (11.6), 4.6 (6.5), and 3.7 (6.4) in patients without a history of receiving bDMARDs; 12.5 (8.7), 9.1 (10.3), and 7.3 (8.8) in those with a history of receiving one bDMARD; and 10.1 (8.5), 5.5 (4.9), and 6.0 (7.2) in those with a history of receiving two or more bDMARDs, respectively (Figures 5a–5c). Significant differences in JADAS-27

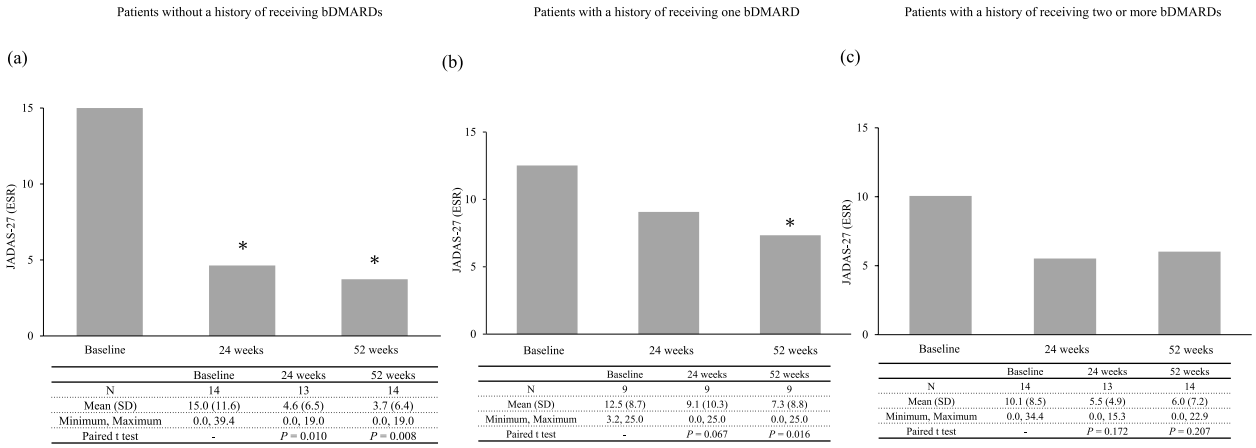


(a)	Baseline	24 weeks	52 weeks
N	4	4	4
Mean (SD)	13.5 (8.7)	8.6 (11.2)	7.8 (11.6)
Minimum, Maximum	5.0, 21.0	0.0, 25.0	0.0, 25.0
Paired t test	-	$P = 0.296$	$P < 0.302$

(b)	Baseline	24 weeks	52 weeks
N	16	16	16
Mean (SD)	8.3 (9.5)	6.6 (8.3)	5.1 (6.7)
Minimum, Maximum	0.0, 27.1	0.0, 25.0	0.0, 19.0
Paired t test	-	$P = 0.467$	$P = 0.177$

(c)	Baseline	24 weeks	52 weeks
N	28	25	28
Mean (SD)	9.6 (9.3)	4.1 (5.7)	4.0 (7.0)
Minimum, Maximum	0.0, 39.4	0.0, 22.2	0.0, 22.9
Paired t test	-	$P = 0.010$	$P = 0.009$

Fig. 4 Time course of JADAS-27 scores and disease activity status according to the ILAR classification. The mean (SD) JADAS-27 scores over time in patients with oligoarticular JIA (**a**), those with RF-negative polyarticular JIA (**b**), and those with RF-positive polyarticular JIA (**c**) are shown. The disease activity status based on JADAS-27 over time in patients with oligoarticular JIA (**d**), those with RF-negative polyarticular JIA (**e**), and those with RF-positive polyarticular JIA (**f**) are shown. A paired t-test was used for statistical analysis, with $P < 0.05$ considered to indicate statistical significance. An asterisk (*) indicates a significant difference was found when compared with baseline. JIA, juvenile idiopathic arthritis; RF, rheumatoid factor; JADAS, Juvenile Arthritis Disease Activity Score; ESR, erythrocyte sedimentation rate



(a)	Baseline	24 weeks	52 weeks
N	14	13	14
Mean (SD)	15.0 (11.6)	4.6 (6.5)	3.7 (6.4)
Minimum, Maximum	0.0, 39.4	0.0, 19.0	0.0, 19.0
Paired t test	-	$P = 0.010$	$P = 0.008$

(b)	Baseline	24 weeks	52 weeks
N	9	9	9
Mean (SD)	12.5 (8.7)	9.1 (10.3)	7.3 (8.8)
Minimum, Maximum	3.2, 25.0	0.0, 25.0	0.0, 25.0
Paired t test	-	$P = 0.067$	$P = 0.016$

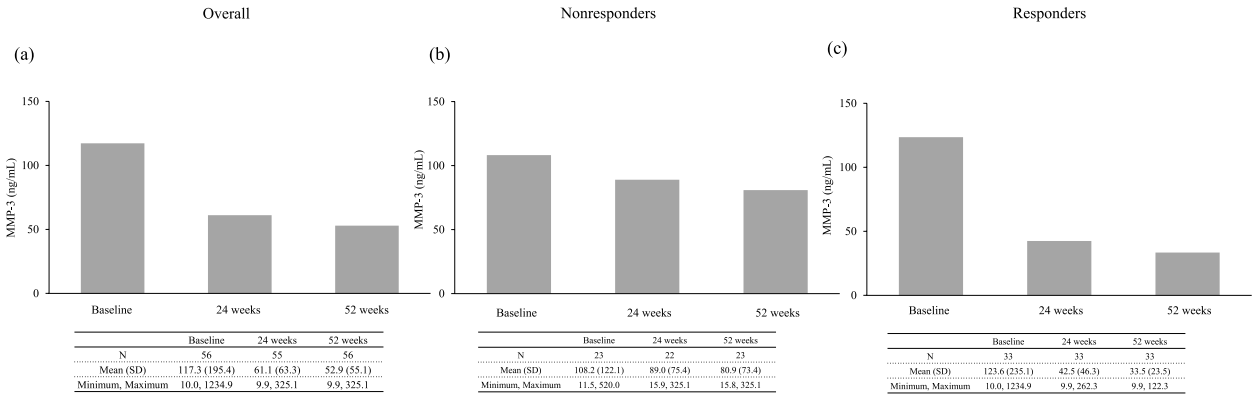
(c)	Baseline	24 weeks	52 weeks
N	14	13	14
Mean (SD)	10.1 (8.5)	5.5 (4.9)	6.0 (7.2)
Minimum, Maximum	0.0, 34.4	0.0, 15.3	0.0, 22.9
Paired t test	-	$P = 0.172$	$P = 0.207$

Fig. 5 Time course in JADAS-27 scores by a history of receiving bDMARDs. The mean (SD) JADAS-27 scores over time in patients without a history of receiving bDMARDs (**a**), those with a history of receiving one bDMARD (**b**), and those with a history of receiving two or more bDMARDs (**c**) are shown. A paired t-test was used for statistical analysis, with $P < 0.05$ considered to indicate statistical significance. An asterisk (*) indicates a significant difference was found when compared with baseline. bDMARD, biologic disease-modifying anti-rheumatic drugs; JADAS, Juvenile Arthritis Disease Activity Score; ESR, erythrocyte sedimentation rate

among patients without a history of receiving bDMARDs were observed between baseline and 24 or 52 weeks after abatacept administration (Figure 5a). Specifically, a significant difference in JADAS-27 among patients with a history of receiving one bDMARD was observed between baseline and 52 weeks after abatacept administration (Figure 5b).

Time course of MMP-3 levels

A decreasing trend in the MMP-3 levels from baseline to 52 weeks after abatacept administration over time was observed for the overall patients and responders, although no statistical test was performed (Figures 6a and 6c). For nonresponders, a slight change was observed



	Baseline	24 weeks	52 weeks
N	56	55	56
Mean (SD)	117.3 (195.4)	61.1 (63.3)	52.9 (55.1)
Minimum, Maximum	10.0, 1234.9	9.9, 325.1	9.9, 325.1

	Baseline	24 weeks	52 weeks
N	23	22	23
Mean (SD)	108.2 (122.1)	89.0 (75.4)	80.9 (73.4)
Minimum, Maximum	11.5, 520.0	15.9, 325.1	15.8, 325.1

	Baseline	24 weeks	52 weeks
N	33	33	33
Mean (SD)	123.6 (235.1)	42.5 (46.3)	33.5 (23.5)
Minimum, Maximum	10.0, 1234.9	9.9, 262.3	9.9, 122.3

Fig. 6 Time course of MMP-3. The MMP-3 levels at baseline and 24 and 52 weeks after administration of abatacept are shown for overall patients (**a**), nonresponders (**b**), and responders (**c**). Responders for abatacept were defined as patients with 2.0 or less in JADAS-27 (CRP) at 52 weeks after abatacept administration with data imputation using the last observation carried forward (LOCF) method. MMP-3, matrix metalloproteinase-3; CRP, C-reactive protein

in the MMP-3 levels over time (Figure 6b). The mean (SD) MMP-3 levels (ng/mL) in the overall patients were 117.3 (195.4) at baseline, 61.1 (63.3) at 24 weeks, and 52.9 (55.1) at 52 weeks after abatacept administration (Figure 6a). For nonresponders and responders, the mean (SD) MMP-3 levels (ng/mL) were 108.2 (122.1) and 123.6 (235.1) at baseline, 89.0 (75.4) and 42.5 (46.3) at 24 weeks, 80.9 (73.4) and 33.5 (23.5) at 52 weeks after abatacept administration, respectively (Figures 6b and 6c).

Effect of abatacept on growth

An increasing trend was observed in the mean (SD) of height and weight SDS over time for the overall patients. For height at baseline, 24 weeks, and 52 weeks, the mean (SD) was −0.43 (1.63), −0.33 (1.69) and −0.07 (1.64), respectively (Table 7a), whereas it was −0.32 (0.98), −0.20 (1.06), and −0.14 (1.01) for weight, respectively (Table 7b).

Similarly, an improving trend was observed in height and weight SDS over time for patients without (Tables 7c and 7d) and with (Tables 7e and 7f) corticosteroids. For changes from baseline in height (overall), weight (overall), and height (without corticosteroid) at 24 weeks and weight (overall) at 52 weeks, the lower limits of 95% confidence intervals were > 0 (Tables 7a–7c).

Discussion

This PMS study is the only real-world prospective study on abatacept in patients with refractory polyarticular-course JIA. The findings obtained from this study will be beneficial for the use of abatacept in Japanese patients with refractory polyarticular-course JIA.

In this study, the proportion of patients with RF-positive polyarticular JIA was 54.9% (45 of 82), whereas those of patients with oligoarticular and RF-negative polyarticular JIA were 12.2% (10 of 82) and 28.0% (23 of 82), respectively. According to the clinical practice guidelines for JIA [8], the proportions of patients with each subtype of JIA based on the ILAR classification in Japan are 41.7% for systemic, 20.2% for oligoarticular, 13.7% for RF-negative polyarticular, and 18.2% for RF-positive polyarticular JIA. Recent epidemiologic research conducted in Japan [9] also reported that among all JIA cases, the proportions of patients were 38.6% for systemic, 22.1% for oligoarticular, 18.4% for RF-negative polyarticular, and 19.5% for RF-positive polyarticular JIA. In these epidemiological studies, the proportion of patients with oligoarticular, RF-negative polyarticular, or RF-positive polyarticular JIA, other than systemic JIA, was approximately the same. This finding suggests that many patients with RF-positive polyarthritis cannot be managed with existing drugs in actual practice, and many of them are being treated with abatacept.

RF- and ACPA-positive polyarthritis is not only difficult to treat with bDMARDs other than abatacept but also a prognostic factor for joint destruction [10–12]. As illustrated in Fig. 4c and Additional files 5 and 6, abatacept showed effectiveness for RF- and ACPA-positive polyarthritis in the same manner as it did for RF-negative polyarthritis. This suggests that abatacept could be an effective therapeutic option for all polyarticular JIA, including RF-positive polyarticular JIA.

Comparing the incidence of ADRs between real-world and clinical trial settings provides a more comprehensive view of abatacept's safety profile. Although directly comparing the incidence of ADRs is challenging owing to different patient backgrounds, the incidences of ADRs (22.0%) and severe ADRs (2.4%) in this study were not higher than those in the phase III study conducted in Japan (IM101-365 study) [6], which were 30.0% (6 of 20)

Table 7 Height and weight SDS

(a) Height (Overall)					(b) Weight (Overall)				
		Baseline	**24 weeks**	**52 weeks**			**Baseline**	**24 weeks**	**52 weeks**
SDS	N	65	60	48	SDS	N	65	61	51
	Mean (SD)	−0.43 (1.63)	−0.33 (1.69)	−0.07 (1.64)		Mean (SD)	−0.32 (0.98)	−0.20 (1.06)	−0.14 (1.01)
	Minimum, Maximum	−6.85, 3.39	−6.67, 2.76	−6.79, 3.65		Minimum, Maximum	−2.02, 2.85	−1.98, 2.46	−2.27, 1.80
Change from baseline	N	-	59	47	Change from baseline	N	-	60	50
	Mean (SD)	-	0.09 (0.33)	0.16 (0.59)		Mean (SD)	-	0.11 (0.32)	0.14 (0.45)
	Minimum, Maximum	-	−0.63, 1.47	−1.27, 2.94		Minimum, Maximum	-	−0.72, 1.06	−1.05, 1.75
	95% CI	-	0.005, 0.176	−0.018, 0.331		95% CI	-	0.030, 0.196	0.015, 0.274
(c) Height (Without oral corticosteroids)					(d) Weight (Without oral corticosteroids)				
		Baseline	24 weeks	52 weeks			Baseline	24 weeks	52 weeks
SDS	N	35	32	27	SDS	N	35	32	28
	Mean (SD)	0.03 (1.23)	0.17 (1.25)	0.42 (1.26)		Mean (SD)	−0.17 (0.97)	−0.05 (0.97)	0.07 (0.96)
	Minimum, Maximum	−3.45, 3.39	−2.80, 2.76	−1.19, 3.65		Minimum, Maximum	−1.82, 2.85	−1.74, 2.12	−1.36, 1.80
Change from baseline	N	-	32	27	Change from baseline	N	-	32	28
	Mean (SD)	-	0.13 (0.37)	0.18 (0.68)		Mean (SD)	-	0.10 (0.32)	0.16 (0.49)
	Minimum, Maximum	-	−0.63, 1.47	−1.27, 2.94		Minimum, Maximum	-	−0.72, 1.06	−1.05, 1.75
	95% CI	-	0.001, 0.267	−0.090, 0.452		95% CI	-	−0.013, 0.220	−0.030, 0.351
(e) Height (With oral corticosteroids)					(f) Weight (With oral corticosteroids)				
		Baseline	24 weeks	52 weeks			Baseline	24 weeks	52 weeks
SDS	N	30	28	21	SDS	N	30	29	23
	Mean (SD)	−0.96 (1.88)	−0.90 (1.96)	−0.70 (1.88)		Mean (SD)	−0.50 (0.98)	−0.38 (1.14)	−0.40 (1.04)
	Minimum, Maximum	−6.85, 1.38	−6.67, 1.40	−6.79, 1.52		Minimum, Maximum	−2.02, 2.31	−1.98, 2.46	−2.27, 1.69
Change from baseline	N	-	27	20	Change from baseline	N	-	28	22
	Mean (SD)	-	0.04 (0.27)	0.12 (0.46)		Mean (SD)	-	0.12 (0.32)	0.13 (0.41)
	Minimum, Maximum	-	−0.38, 0.66	−0.62, 1.17		Minimum, Maximum	-	−0.31, 1.06	−0.88, 0.93
	95% CI	-	−0.067, 0.144	−0.092, 0.339		95% CI	-	−0.001, 0.249	−0.059, 0.309

SD standard deviation, *SDS* standard deviation score, *CI* confidence interval

and 5.0% (1 of 20), respectively. In this study, no ADRs with particularly high incidence were observed compared to those during the clinical trial. These results indicate that the safety profile of abatacept does not markedly differ between the clinical trial and real-world settings.

A decreasing trend was observed over time for JADAS-27, and disease activity improved, confirming that abatacept is effective for refractory polyarticular-course JIA. In the phase III IM101-365 study, the mean JADAS-27 score at baseline was 13.9 with no patients in remission (JADAS-27 score < 1), and the mean change from baseline in JADAS-27 score was −10.8 at week 52 with 50% of patients in remission; the mean JADAS-27 score and disease activity gradually decreased over time from baseline to week 52 [6]. This indicates that the results obtained from the clinical trial are also applicable in real-world settings.

In addition to the clinical effectiveness, patients for whom the treatment with abatacept was particularly effective showed a decreasing trend in MMP-3 levels. Since MMP-3 plays an important role in the pathology of inflammatory joint diseases [13], these results suggest that inflammation within the joints was also suppressed due to the inhibition of T-cell activation. Since steroid administration is known to increase MMP-3 levels [14], the observed decreasing trend in MMP-3 levels may be influenced by reduction or discontinuation of steroid administration.

Discontinuing or decreasing steroids is a significant challenge for patients with JIA. Thirty-six patients received oral corticosteroids at the start of abatacept administration in this study. Fourteen patients discontinued concomitant use during the treatment period; however, none discontinued treatment because of adverse

events. In adult rheumatoid arthritis, a report has shown that abatacept enables the reduction or discontinuation of glucocorticoids [15] and allows some patients with polyarticular-course JIA to reduce or discontinue corticosteroids.

Growth retardation induced by JIA may be caused by joint inflammation and/or corticosteroids. In this study, improvement in both height and weight SDS were observed in patients who were treated with abatacept. This is partly attributed to the fact that the combination rate and dose of corticosteroids were reduced due to the administration of abatacept. Additionally, the suppression of T cell activation by abatacept may alleviate systemic inflammation, thereby preventing adverse effects on growth [16, 17]. Abatacept may also have the potential to restore growth, making it a promising treatment option for patients with polyarticular-course JIA in their growth phase.

However, this study has some limitations because it is a non-interventional survey conducted under real-world conditions. First, the study lacked a control group, and no detailed inclusion or exclusion criteria were established for target patients. Second, the Childhood Health Assessment Questionnaire, which is the most widely used functional health status measure, was not used. Third, factors other than height and weight, which affect a child's growth were not evaluated. Fourth, because laboratory test measurements were not required at the start of treatment, baseline values were unknown or unrecorded in many patients. Fifth, the observation period for the study was predetermined as part of the postmarketing surveillance plan. Therefore, the safety profile of abatacept for long-term use exceeding one year (52 weeks) was not evaluated. Finally, the use of concomitant drugs was unlimited.

Conclusions

Abatacept is usually administered to patients with RF-positive polyarticular-course JIA, who are challenging to treat with other drugs. The incidence of ADRs during real-world use was not higher than that reported in the clinical trials; therefore, abatacept is effective in treating refractory polyarticular-course JIA in the real world. Furthermore, abatacept has been shown to restore a child's growth. These results suggest that abatacept is a useful therapeutic option for the treatment of refractory polyarticular-course JIA in real-world settings in Japan.

Abbreviations

ACPA	Anti-citrullinated protein antibody
ADRs	Adverse drug reactions
bDMARDs	Biologic disease-modifying anti-rheumatic drugs
IL	Interleukin
ILAR	International League of Associations for Rheumatology
JADAS-27	Juvenile Arthritis Disease Activity Score 27
JIA	Juvenile idiopathic arthritis
LOCF	Last observation carried forward
MMP-3	Matrix metalloproteinase-3
MTX	Methotrexate
PMS	Postmarketing surveillance
PT	Preferred term
RF	Rheumatoid factor
SD	Standard deviation
SDS	Standard deviation scores
SOC	System organ class
TNF-α	Tumor necrosis factor-α

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12969-025-01069-4.

Additional file 1: The table shows the data on RF, ACPA, MMP-3, and antinuclear antibody levels at baseline in the safety analysis set

Additional file 2: The table shows the data on ACPA at baseline according to the ILAR classification in the effectiveness analysis set

Additional file 3: The figure shows the probability of continuation of MTX from the start of treatment with abatacept by the Kaplan–Meier method

Additional file 4: The table shows the data on timing of onset of adverse drug reactions which occurred in newly treated patients. Adverse drug reactions were coded using MedDRA version 24.0 and summarized by SOC and PT. If the same PT occurred multiple times in the same patient, only the PT which occurred first was counted

Additional file 5: The table shows the data on JADAS-27 scores at baseline, 24 weeks, and 52 weeks and the changes in JADAS-27 scores from baseline in patients with RF- and ACPA negative/positive polyarthritis

Additional file 6: The table shows the data on the number and proportion of patients by disease activity at baseline, 24 weeks, and 52 weeks in patients with RF- and ACPA- negative/positive polyarthritis

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Authors' contributions

T.N., I.K., N.I., T.I., S.O., E.B., T.Y., K.H., and S.T. contributed to the study conception and design. S.T., T.N., N.T., N.I., T.I., and I.K. contributed to data acquisition. E.B. and N.I. contributed to data analysis. T.N., N.T., N.I., I.K., S.O., T.Y., E.B., K.H., and S.T. contributed to data interpretation. All authors contributed to the critical revision of the manuscript, approved the final draft, and are accountable for the accuracy or integrity of the work.

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Data availability

Bristol Myers Squibb's policy on data sharing may be found at https://www.bms.com/researchers-and-partners/clinical-trials-and-research/disclosure-commitment.html.

Declarations

Ethics approval and consent to participate

This PMS study was conducted in accordance with Good Postmarketing Surveillance Practices and the ethical principles of the Declaration of Helsinki. Informed consent was obtained from all participants in the study. The ethics review board of each participating institution approved this study.

Consent for publication

Not applicable.

Competing interests
N. I. received honoraria for lectures from AbbeVie GK, Mitsubishi Tanabe Pharma Corporation, and GlaxoSmithKline K.K. and for serving as a moderator from AYUMI Pharmaceutical Corporation. S. T. received research grants from Chugai Pharmaceutical Co. Ltd. and honoraria for speakers' bureaus from AbbVie GK, AstraZeneca plc, Astellas Pharma Inc., AYUMI Pharmaceutical Corporation, Chugai Pharmaceutical Co. Ltd., Eisai Co., Ltd., GlaxoSmithKline K.K., Mitsubishi Tanabe Pharma Corporation, Novartis Pharmaceuticals, and ONO PHARMACEUTICAL CO., LTD. S.O., T. Y., E.B., and K.H. are employees of Bristol Myers Squibb and own stock in Bristol Myers Squibb. All other authors declare no conflicts of interest associated with this manuscript.

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