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Clinical remission rate and drug withdrawal status in articular juvenile idiopathic arthritis

Akira Oshima[1*], Takasuke Ebato[2], Masanori Kaneko[2], Yoshiaki Shikama[1] and Tomoyuki Imagawa[1]

Abstract

Background The clinical remission rate of articular juvenile idiopathic arthritis (JIA) differs according to the disease categories. At present, there is no consensus regarding drug withdrawal after remission is achieved.

Objectives To clarify the clinical remission rate and drug withdrawal status of patients with juvenile idiopathic arthritis (JIA).

Methods We conducted a retrospective observational study in patients who developed articular JIA by 2017 and were followed up (2013–2022). The Wallace criteria were used as remission criteria.

Results Forty-nine patients were included, i.e., 16 (33%) with polyarticular JIA (PJIA) and 33 (67%) with oligoarticular JIA (OJIA). Rheumatoid factor-positive (RF +) PJIA had significantly higher biological disease-modifying antirheumatic drug (bDMARD) introduction rates (86%, $p < 0.01$). The rate of clinical remission off medication was significantly higher in OJIA (67%). Numerous cases of RF + PJIA (50%), RF-negative (RF –) PJIA (25%), and OJIA (30%) flared within 2 years after conventional synthetic disease-modifying antirheumatic drug withdrawal. Patients with RF – PJIA and OJIA (two cases each) discontinued bDMARDs. Both RF – PJIA cases (100%) and half of OJIA cases (50%) flared within 2 years after bDMARD withdrawal. In one case of OJIA, remission was maintained after withdrawal of all drugs.

Conclusions OJIA had the highest rate of clinical remission off medication (67%) versus others. In OJIA, it was possible to discontinue all drugs in some patients with OJIA receiving bDMARDs. In PJIA requiring bDMARDs, withdrawal of bDMARDs was difficult all two cases.

Keywords Drug withdrawal, Juvenile idiopathic arthritis, Outcome, Remission

Introduction

Articular juvenile idiopathic arthritis (JIA) is classified into the following disease categories according to the revised International League Against Rheumatism classification criteria. Oligoarticular juvenile idiopathic arthritis (OJIA) affects up to four joints within 6 months after onset and is further divided into two types: extended (progression to five or more affected joints beyond 6 months after onset) and persistent (up to four affected joints throughout the entire course of the disease). Polyarticular juvenile idiopathic arthritis (PJIA) is a form of JIA with five or more affected joints within 6 months after onset, which is further divided into rheumatoid factor-negative (RF –) and rheumatoid factor-positive (RF +) PJIA based on the presence or absence of RF. Other categories include psoriatic arthritis (PsA), enthesitis-related arthritis (ERA), and undifferentiated arthritis [1].

The Japan College of Rheumatology has published guidelines for the initial treatment of Juvenile Idiopathic Arthritis (JIA). The treatment for articular JIA includes non-steroidal anti-inflammatory drugs (NSAIDs), conventional synthetic DMARDs (csDMARDs) such as

*Correspondence:
Akira Oshima
ooshima.4u00k@kanagawa-pho.jp
[1] Department of Infectious Disease & Immunology, Kanagawa Children's Medical Center, Yokohama 232-8555, Japan
[2] Department of Pediatrics, Kitasato University School of Medicine, Sagamihara 252-0375, Japan

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methotrexate (MTX), glucocorticoids (GC) administered systemically or via intra-articular injection, and biological disease-modifying antirheumatic drugs (bDMARDs) such as tocilizumab (TCZ), adalimumab (ADA) and etanercept (ETN). MTX is recommended as the initial treatment for high-risk groups. The high-risk group is defined by meeting one or more of the following conditions: 1) positive for anti-cyclic citrullinated peptide antibody (ACPA) or rheumatoid factor (RF); 2) elevated inflammatory markers (C-reactive protein levels or erythrocyte sedimentation rate twice the normal level) accompanied by arthritis in the hand or ankle; 3) presence of cervical or hip lesions; 4) imaging showing bone destruction and bone marrow edema. If clinical remission is not achieved following initial treatment with MTX, the introduction of bDMARDs is recommended [2].

The development of these treatment strategies has enabled more patients with JIA to achieve clinical remission. Long-term clinical remission on medication has the advantage of reducing joint destruction caused by arthritis. However, continuous long-term administration of medications may have some disadvantages for patients who achieved inactive disease (ID), such as drug-related adverse events, frequent hospital visits and financial burden [3]. For instance, MTX, an important drug for the treatment of JIA, rarely causes serious adverse events, but gastrointestinal symptoms such as abdominal discomfort and vomiting occur with some frequency are associated with MTX intolerance, which increases with the duration of MTX treatment and can adversely affect patients' quality of life [4]. In bDMARDs, current evidence does not support an increased risk of malignancy or immunological disorders. However, in terms of infections, a slight increase in infections is reported [5].

The clinical remission off medication (CR) rate of JIA differs according to the disease categories. OJIA is associated with a higher likelihood of CR than PJIA [6]. On the other hand, some patients experience flare after drug withdrawal [7, 8]. Among patients who achieved ID and discontinued MTX, 58.2% reported a relapse within one year [9]. In another report, 75.6% of patients who achieved ID relapsed after discontinuing treatment, with a median follow-up time to remission off therapy of 6 months [7]. Therefore, it is important to balance the benefits and risks associated with medications, as well as identify the patients in whom a drug can be discontinued. However, at present, there is no consensus regarding drug withdrawal after remission is achieved [3]. Thus, we conducted a retrospective observational study to clarify the clinical remission rate and drug withdrawal status at our institution.

Materials and methods

The diagnosis of JIA was based on the revised International League Against Rheumatism classification criteria [1]. We conducted a retrospective observational study in patients who developed articular JIA between 2002 and 2017 and were followed up in our department at Kanagawa Children's Medical Center (Yokohama, Japan) from January 1, 2013, to September 30, 2022. We extracted data from the electronic medical records, such as JIA disease categories, age of onset, sex, antinuclear antibody (ANA) positivity rate, anti-cyclic citrullinated peptide antibody (ACPA) positivity rate, history of uveitis, duration of follow-up, use and duration of non-steroidal anti-inflammatory drugs, glucocorticoids, conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) such as methotrexate (MTX), biological disease-modifying antirheumatic drugs (bDMARDs), types of bDMARDs, disease activity at the end of observation, flare rate and time to flare, drug withdrawal methods (immediate discontinuation or prolonged dosing interval), and response after flare. ANA positivity was defined by a titre above 1:160 [10]. Values $\geq$ 15 IU/mL indicated RF+. The following patients were excluded; 1) the patients who were not recorded in the electronic medical record (introduced in our hospital in 2013) and whose past course could not be traced back, 2) systemic JIA, 3) patients with onset after 2018; we considered that the duration of ID was so short that they did not try withdrawal of medication, and that even if they did, the observation period would be insufficient to assess flare after withdrawal of medication. ERA was not included as there was only one person during the period and the sample was too small to analyze. Patients with psoriatic arthritis or undifferentiated arthritis did not have any patients and were not included in the results.

The Wallace criteria were used as remission criteria [11]. ID was defined by: 1) absence of joints with active arthritis; 2) absence of fever, rash, serositis, splenomegaly, or generalized lymphadenopathy attributable to JIA; 3) absence of active uveitis; 4) normal erythrocyte sedimentation rate or C-reactive protein levels (if both are tested, both must be within the normal range); and 5) a physician's global assessment of disease activity indicating no disease activity. Clinical remission on medication (CRM) was defined as continued ID on medication for $\geq$ 6 consecutive months. Clinical remission off medication (CR) was defined as continued ID after withdrawal of all medications for $\geq$ 12 consecutive months. Flare was defined by not meeting the criteria for ID.

We have in-house conditions for the withdrawal of medication. In our hospital, the conditions for the withdrawal of csDMARDs and bDMARDs are as follows: CRM must be achieved; ID must be maintained

for ≥ 12 months; and the patient must agree and wish to withdraw the medication. We also consider the categories of JIA and the social circumstances of the patients.

Statistical analysis

All statistical analyses were performed with EZR version Mac OS X 1.61 (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria) [12]. *P*-values < 0.05 denoted statistical significance. The Kruskal–Wallis test and Steel–Dwass multiple comparisons were used for comparisons among the three groups.

Ethics approval

This study was approved by the Ethics Committee of Kanagawa Children's Medical Center (approval number: 145–2). Because of the retrospective nature of this study, the Ethics Committee of our institution determined that it was not necessary to obtain written informed consent for this study from the patients/guardians. The documents explaining the study and opt-out documents were available on the website of our institution. No patient offered to decline after the opt-out document was published. This study was conducted in accordance with consensus ethical principles from an appropriate version of the World Medical Association Declaration of Helsinki-Ethical Principles for Medical Research Involving Human Subjects.

Results

Patients

As shown in Fig. 1, 75 patients were diagnosed with articular JIA. Cases with disease onset after 2018 or missing data or a patient with ERA were excluded. Finally, 49 eligible patients were included in the analysis: 16 (33%) and 33 (67%) with PJIA and OJIA, respectively. PJIA was further divided into RF + (n = 7 [14%]) and RF − (n = 9 [18%]); OJIA was extended and persistent in one (2%) and 32 (65%) patients, respectively.

Patient characteristics are shown in Table 1. The median year of onset was 2013 (2002–2017) overall, 2011 (2010–2015) for RF + PJIA, 2014 (2002–2016) for RF − PJIA and 2013 (2005–2017) for OJIA (p = 0.43). The age of onset was significantly lower in OJIA (median age: 2 years, p < 0.01), and RF + PJIA was associated with a significantly higher rate of ACPA positivity (71%, p < 0.01), long MTX durations (median: 87 months, p < 0.05), and high bDMARD introduction rates (86%, p < 0.01). There were no significant differences in terms of sex, ANA positivity, history of uveitis, or the duration of follow-up. Although there were no significant differences observed, the duration of GC and bDMARD administration tended to be longer in PJIA than in OJIA. The median duration of GC administration was 19 (10–46), 44 (12–65), and 8 (4–54) months in RF + PJIA, RF − PJIA, and OJIA, respectively (p = 0.06). GC was administered in 6 (86%) patients of RF + PJIA, 9 (100%) patients of RF − PJIA and 27 (84%) patients of OJIA. All patients in which GC was administered received systemic steroids, including one case (2%) of OJIA in which intra-articular injections were performed in the USA. The median duration of bDMARD administration was 100 (84–109), 92 (86–93), and 60 (34–100) months, respectively (p = 0.11).

Types of bDMARDs

The bDMARDs administered were tocilizumab (TCZ), infliximab (IFX), adalimumab (ADA), and abatacept

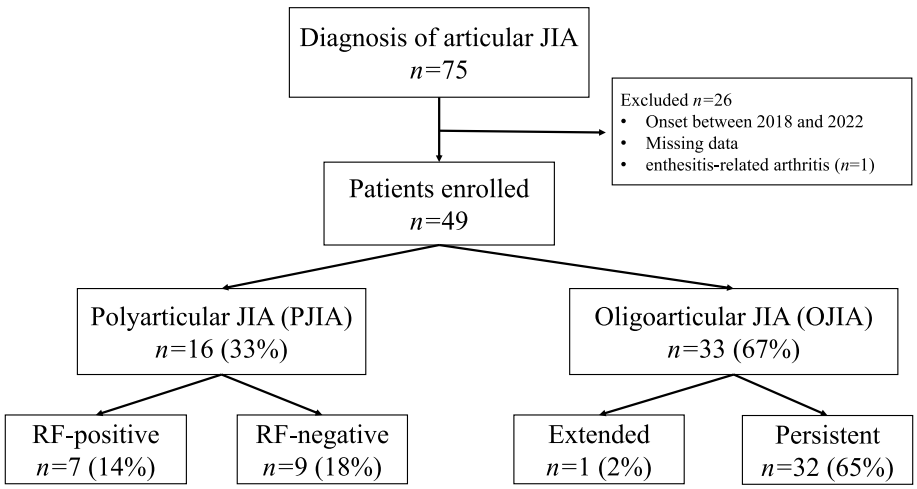

Fig. 1 CONSORT diagram. RF positivity was defined by values ≥ 15 IU/mL. JIA, juvenile idiopathic arthritis; RF, rheumatoid factor

Table 1 Patient characteristics

	RF + PJIA (*n* = 7 [14%])	RF − PJIA (*n* = 9 [18%])	OJIA (*n* = 33 [67%])	*p*-value
Year of onset (year)	2011 (2010–2015)	2014 (2002–2016)	2013 (2005–2017)	0.43
Age of onset (years)	12 (11–12)	11 (2–13)	2 (1–12)	< 0.01[c]
Female	7 (100%)	6 (67%)	27 (82%)	0.24
Male	0 (0%)	5 (33%)	25 (18%)	0.24
ANA-positive	1 (14%)	2 (22%)	12 (36%)	0.34
ACPA-positive	5 (71%)	0 (0%)	0 (0%)	< 0.01[d]
History of uveitis	0 (0%)	0 (0%)	4 (12%)	0.36
Follow-up duration (months)	124 (76–129)	75 (25–133)	56 (16–177)	0.15
Drug administered				
NSAIDs	7 (100%)	8 (89%)	31 (97%)	0.67
Duration of administration[a] (months)	24 (12–73)	28 (12–49)	9.5 (1–107)	0.54
Glucocorticoids[a]	6 (86%)	9 (100%)	27 (84%)	0.17
Duration[b] (months)	19 (10–46)	44 (12–65)	8 (4–54)	0.06
Methotrexate	7 (100%)	9 (100%)	33 (100%)	Null
Duration of administration[a] (months)	87 (12–118)	38 (2–95)	20 (4–146)	< 0.05[e]
bDMARDs	6 (86%)	4 (44%)	7 (22%)	< 0.01[f]
Duration of administration[a] (months)	100 (84–109)	92 (86–93)	60 (34–100)	0.11

Data are presented as the median (range) or *n* (%), unless otherwise indicated

ACPA anti-cyclic citrullinated peptide antibody, *ANA* antinuclear antibody, *bDMARDs* biological disease-modifying antirheumatic drugs, *NSAIDs* non-steroidal anti-inflammatory drugs, *OJIA* oligoarticular juvenile idiopathic arthritis, *PJIA* polyarticular juvenile idiopathic arthritis, *RF* rheumatoid factor

[a] Intra-articular injections were performed in the USA only in one case of OJIA; the other patients received systemic glucocorticoids

[b] Continuing cases are calculated based on the period up to September 30, 2022

[c] OJIA versus RF + PJIA, *p*-value < 0.01, OJIA versus RF − PJIA, *p*-value < 0.01. RF + PJIA versus RF − PJIA, *p*-value = 0.27. [d] RF + PJIA versus RF − PJIA, *p*-value < 0.01. RF + PJIA versus OJIA, *p*-value < 0.01. [e] RF + PJIA versus OJIA, *p*-value < 0.05. RF + PJIA versus RF − PJIA, *p*-value 0.32. OJIA versus RF − PJIA, *p*-value 0.58. [f] RF + PJIA versus RF − PJIA, *p*-value 0.22. RF + PJIA versus OJIA, *p*-value < 0.01. OJIA versus RF − PJIA, *p*-value 0.35

(ABT) (Table 2). Overall, of the 17 patients who received bDMARDs, 13 (76%), one (6%), six (35%), and two (12%) received TCZ, IFX, ADA, and ABT, respectively. Of the patients with RF + PJIA (*n* = 6 [86%]), five (83%), three (50%), and one (17%) received TCZ, ADA, and ABT, respectively. Of those with RF − PJIA (*n* = 4 [44%]), three (75%), one (25%), and one (25%) received TCZ, ADA, and ABT, respectively. Among patients with OJIA (*n* = 7 [22%]), five (71%), one (14%), and two (28%) received TCZ, IFX, and ADA, respectively. TCZ was the most frequently administered drug in all disease types. No patients were treated with etanercept (ETN) in any of the disease types. There were no significant differences among disease types for any of the drugs.

Disease activity at the end of observation

As shown in Table 3, CRM was significantly more common in RF + PJIA (86%), while CR was more common in OJIA (67%). Of the six patients (86%) with RF + PJIA who achieved CRM, three patients (43%) were still

Table 2 Types of bDMARDs administered

Type of bDMARD	Overall (*n* = 17 [35%])	RF + PJIA (*n* = 6 [86%])	RF − PJIA (*n* = 4 [44%])	OJIA (*n* = 7 [22%])	*p*-value
Tocilizumab	13 (76%)	5 (83%)	3 (75%)	5 (71%)	0.89
Infliximab	1 (6%)	0	0	1 (14%)	0.49
Adalimumab	6 (35%)	3 (50%)	1 (25%)	2 (28%)	0.66
Abatacept	2 (12%)	1 (17%)	1 (25%)	0	0.44

Data are presented as *n* (%)

bDMARD biological disease-modifying antirheumatic drug, *OJIA* oligoarticular juvenile idiopathic arthritis, *PJIA* polyarticular juvenile idiopathic arthritis, *RF* rheumatoid factor

Table 3 Disease activity at the end of observation

	RF + PJIA (*n* = 7 [14%])	RF − PJIA (*n* = 9 [18%])	OJIA (*n* = 33 [67%])	*p*-value
Active disease	0	0	1 (3%)[b]	0.79
Inactive disease	0	0	2 (9%)[c]	0.61
CRM	6 (86%)	4 (44%)	5 (15%)	< 0.01[e]
bDMARDs + csDMARDs	3 (43%)	2 (22%)	1 (3%)	-
bDMARDs	3 (43%)	2 (22%)	0 (0%)	-
bDMARDs + csDMARDs + GC	0	0	1 (3%)	-
No medication	0	0	3 (9%)[d]	-
CR	1 (14%)[a]	5 (56%)	22 (67%)	< 0.05[f]

Data are presented as *n* (%), unless otherwise indicated

ACPA anti-cyclic citrullinated peptide antibody, *bDMARD* biological disease-modifying antirheumatic drug, *CR* clinical remission off medication, *CRM* clinical remission on medication, *csDMARD* conventional synthetic disease-modifying antirheumatic drug, *GC* glucocorticoid, *OJIA* oligoarticular juvenile idiopathic arthritis, *PJIA* polyarticular juvenile idiopathic arthritis, *RF* rheumatoid factor

[a] ACPA-negative case

[b] One patient with OJIA presented with active uveitis and had active disease

[c] In both cases, bDMARDs were introduced after flare on csDMARDs monotherapy and ID was achieved with a combination of bDMARDs and csDMARDs

[d] < 12 months after discontinuation of all medications

[e] RF + PJIA versus RF − PJIA, *p*-value 0.22. RF + PJIA versus OJIA, *p*-value < 0.01. RF − PJIA versus OJIA, *p*-value 0.15

[f] RF + PJIA versus RF − PJIA, *p*-value 0.23. RF + PJIA versus OJIA, *p*-value < 0.05. RF − PJIA versus OJIA, *p*-value 0.82

receiving a combination of bDMARDs and csDMARDs, and three patients (43%) were still receiving bDMARDs alone. The one patient with RF + PJIA who achieved CR was an ACPA-negative case. One patient with OJIA presented with active uveitis and had active disease. The two patients who reached ID in the OJIA were both introduced to bDMARDs after experiencing a flare on csDMARDs monotherapy and achieved ID with a combination of bDMARDs and csDMARDs.

Withdrawal of csDMARDs

Table 4 shows that csDMARDs were withdrawn in four (57%), eight (89%), and 27 (82%) patients with RF + PJIA, RF − PJIA, and OJIA, respectively. The median duration of treatment with csDMARDs was 27 (12–118), 28 (2–76), and 19 (4–128) months for RF + PJIA, RF − PJIA, and OJIA, respectively ($p = 0.81$). The flare rates following csDMARD withdrawal were 50%, 25%, and 30% in RF + PJIA, RF − PJIA, and OJIA, respectively ($p = 0.67$). The median time to flare after csDMARD withdrawal was 4.5 (0–9), 14 (14–14), and 4 (1–30) months for RF + PJIA, RF − PJIA, and OJIA, respectively ($p = 0.17$). Some patients flared after 6 years. Introduction of bDMARDs after flare was significantly more common in RF + PJIA ($p < 0.05$); bDMARDs were initiated in two (100%), zero (0%), and one (13%) patients with RF + PJIA, RF − PJIA, and OJIA, respectively.

No patients with RF + PJIA had prior withdrawal of bDMARDs. One of the four (57%) patients who were withdrawn from csDMARDs was on concomitant use with bDMARDs, while the remaining three patients were not on concomitant use and had no history of administration of bDMARDs. In other words, these three patients were withdrawn from all drugs. In two of the four patients from whom csDMARDs were withdrawn, the reason for withdrawn of csDMARDs was adverse events, and both cases subsequently flared, leading to the introduction of bDMARDs. One of the four patients was on bDMARDs and csDMARDs combination therapy, followed by csDMARDs withdrawal initially and then bDMARDs monotherapy. The remaining one patient had no flares after csDMARDs withdrawal and achieved CR. All three RF + PJIA patients with CRM at the end of observation were treated with bDMARDs monotherapy (TCZ 2 patients, ABA 1 patient).

Of the eight (89%) RF − PJIA patients who discontinued csDMARDs, three were receiving concomitant bDMARDs; all three had previously discontinued csDMARDs due to adverse events and were receiving bDMARDs monotherapy. Three (38%) RF − PJIA patients with CRM at the end of observation were receiving bDMARDs (TCZ monotherapy 2 patients, TCZ + sulfasalazine 1 patient); all five (63%) RF-PJIA patients who achieved CR had not previously received bDMARDs.

There were 27 (82%) patients with OJIA who were discontinued from csDMARDs, 8 (30%) flared after a median of 4 months (1–30), 22 (81%) achieved CR. Of the 22 OJIA patients who achieved CR, no patients received bDMARDs. At the time of csDMARD withdrawal, one patient was treated with concomitant bDMARDs and

Table 4 Cases of csDMARD withdrawal

	RF + PJIA (*n* = 4 [57%])	RF − PJIA (*n* = 8 [89%])	OJIA (*n* = 27 [82%])	*p*-value
Concomitant use of bDMARDs at withdrawal of csDMARDs, *n* (%)	1 (25%)	3 (38%)	1 (4%)	< 0.05 [g]
History of bDMARDs use at withdrawal of csDMARDs, *n* (%)	0 (0%)	0 (0%)	1 (4%)	0.80
Duration of csDMARD administration (months)	27 (12–118)	28 (2–76)	19 (4–128)	0.81
Reasons for withdrawal of csDMARDs				
Adverse event[a], *n* (%)	2 (50%)	4 (50%)	1 (4%)	< 0.05 [h]
Flare after drug withdrawal of csDMARDs, *n* (%)	2 (50%)	2 (25%)	8 (30%)	0.67
Time to flare (months)	4.5 (0–9)	14 (14–14)	4 (1–30)	0.17
Introduction of bDMARDs after flare	2 (100%)	0 (0%)	1 (13%)	< 0.05[i]
Disease activity at the end of observation				
Active disease	0	0	1 (4%)	0.8
Inactive disease	0	0	1 (4%)	0.8
Clinical remission on medication	3 (75%)[b]	3 (38%)[d]	3 (11%)[f]	< 0.05[j]
Clinical remission off medication	1 (25%)[c]	5 (63%)[e]	22 (81%)[e]	0.06

Data are presented as the median (range) or *n* (%), unless otherwise indicated

bDMARD biological disease-modifying antirheumatic drug, *csDMARD* conventional synthetic disease-modifying antirheumatic drug, *OJIA* oligoarticular juvenile idiopathic arthritis, *PJIA* polyarticular juvenile idiopathic arthritis, *RF* rheumatoid factor

[a] Adverse events include MTX intolerance due to gastrointestinal symptoms such as vomiting and nausea, oral aphthae, and liver disorders

[b] All three patients were treated with bDMARDs monotherapy. Two were treated with TCZ, and one with ABA

[c] This patient had not previously received bDMARDs

[d] All three patients were treated with TCZ. Two were treated with TCZ monotherapy, and one with TCZ and sulfasalazine combination therapy after flare following discontinuation of MTX due to adverse effects

[e] None of the patients had received bDMARDs

[f] In three patients, all medications were discontinued; however, the criteria for CR were not achieved by the conclusion of the observation period. One patient initially discontinued TCZ and sustained CRM for one year on MTX monotherapy, after which MTX was also discontinued

[g] RF + PJIA versus RF − PJIA, *p*-value 0.41. RF + PJIA versus OJIA, *p*-value 0.25. RF − PJIA versus OJIA, *p*-value < 0.05. [h] RF + PJIA versus RF − PJIA, *p*-value 1.0. RF + PJIA versus OJIA, *p*-value < 0.05. RF − PJIA versus OJIA, *p*-value < 0.05. RF − PJIA versus OJIA, *p*-value < 0.05. [i] RF + PJIA versus RF − PJIA, *p*-value < 0.09. RF + PJIA versus OJIA, *p*-value < 0.05. RF − PJIA versus OJIA, *p*-value 0.84. [j] RF + PJIA versus RF − PJIA, *p*-value 0.47. RF + PJIA versus OJIA, *p*-value < 0.01. RF − PJIA versus OJIA, *p*-value 0.20

one patient had a history of bDMARDs. One patient with extended OJIA was treated with concomitant bDMARDs at the time of csDMARD withdrawal. The csDMARDs were withdrawn due to adverse events. CRM was then maintained on bDMARDs monotherapy for more than 2 years. The other patient with a history of receiving bDMARDs was treated with a combination of csDMARDs and bDMARDs, then bDMARDs were initially withdrawn and CRM was maintained on csDMARDs monotherapy for one year, after which csDMARDs were also withdrawn.

Withdrawal of bDMARDs

The bDMARDs were withdrawn (Table 5) in patients with RF − PJIA and OJIA (two cases each); notably, withdrawal of bDMARDs did not occur in any patients with RF + PJIA. CRM was maintained for approximately 33 months before bDMARD withdrawal, and for 65 months in the longest case. Nevertheless, the rate of flare after withdrawal was high, occurring in two cases (100%) of RF − PJIA and one case (50%) of OJIA within 1–2 years.

Both 2 patients with RF − PJIA who were withdrawn from bDMARDs had previously been withdrawn from csDMARDs due to adverse events. Both patients were on the subcutaneous autoinjector formulation; CRM was maintained for 65 months on TCZ monotherapy and 34 months on ADA monotherapy, but flares occurred at 7 and 5 months after bDMARD withdrawal, respectively, and bDMARDs were restarted. The method of bDMARD withdrawal was immediate discontinuation.

There were two patients with OJIA who were withdrawn from bDMARDs. One patient was extended OJIA, and the other persistent OJIA. The patients with extended OJIA and maintained CRM on bDMARDs (TCZ) monotherapy for 33 months after withdrawal of csDMARDs due to adverse events, and TCZ was withdrawn. The withdrawal method was done by immediate discontinuation. The patient flared at 23 months and TCZ was reintroduced. The other patient with persistent OJIA maintained CRM with a combination of csDMARDs and bDMARDs for 32 months, then bDMARDs were initially withdrawn and CRM was maintained on csDMARDs monotherapy for one year, after which csDMARDs were

Table 5 Cases of bDMARD withdrawal

	RF − PJIA (*n* = 2 [50%])	**OJIA (*n* = 2 [29%])**
Concomitant use of csDMARDs at withdrawal of bDMARDs, *n* (%)	0 (0%)	1 (50%)
History of csDMARDs use at withdrawal of bDMARDs, *n* (%)	2 (100%)[a]	1 (50%)[a]
CRM duration before drug withdrawal (months)		
Case 1	65	32
Case 2	34	33
Type of bDMARD withdrawn, *n*		
Adalimumab	1[b]	0
Tocilizumab	1[b]	2[c]
Method of drug withdrawal, *n*		
Immediate discontinuation	2	1
Prolonged dosing interval	0	1
With flare, *n* (%)	2 (100%)	1 (50%)
Time to flare (months)		
Case 1	7	23
Case 2	5	-
Response after relapse, *n*		
Switch to other bDMARDs	1[d]	0
Resumed same bDMARDs	1	1
Disease activity at the end of observation, *n*		
Active disease	0	1
CRM	2	1 (no medication)[e]

bDMARD biological disease-modifying antirheumatic drug, *CRM* clinical remission on medication, *csDMARD* conventional synthetic disease-modifying antirheumatic drug, *OJIA* oligoarticular juvenile idiopathic arthritis, *PJIA* polyarticular juvenile idiopathic arthritis, *RF* rheumatoid factor

[a] Discontinuation due to adverse events

[b] Subcutaneous injection

[c] Intravenous injection

[d] Changed from adalimumab to tocilizumab

[e] This patient was withdrawn from all medications; however, the criteria for CR were not achieved by the conclusion of the observation period. This patient initially discontinued TCZ and sustained CRM for one year on MTX monotherapy, after which MTX was also discontinued

also withdrawn. The method of bDMARDs withdrawal was prolonged doing interval. This patient with persistent OJIA was able to discontinue all medications but was included in the CRM category as the CR criteria were not met at the end of the observation period.

Discussion

The results of this study revealed that 14%, 56%, and 67% of patients with RF + PJIA, RF − JIA, and OJIA achieved CR ($p < 0.05$), respectively, with OJIA linked to a significantly higher CR achievement rate. Previously reported CR rates were 0–33%, 22–52%, 13–50%, and 43–80% in RF + PJIA, RF − PJIA, extended OJIA, and persistent OJIA, respectively [13–16]. Our results showed a similar trend to those reported by Selvaag et al. (17%, 52%, 50%, and 80% in RF + PJIA, RF − PJIA, extended OJIA, and persistent OJIA, respectively) [16].

In this study, patients with all disease types received NSAIDs, GCs and csDMARDS (MTX). The median year of onset in this study was 2013, suggesting that most patients were treated according to the 2007 JCR guidelines, which also recommended NSAIDs and MTX as initial treatment. This guidelines commented on GC in the following uses; 1) oral prednisolone (daily dose 0.1 to 0.2 mg/kg, the initial maximum dose approximately 15 mg/day, depending on age and clinical conditions) is sometimes added early in the MTX treatment, 2) During this therapy, the dose of oral prednisolone is gradually decreased to reach the maintenance dose (0.1 mg/ kg per day or 3 to 5 mg/day for school-age or older children) when low-dose methotrexate pulse therapy becomes effective, which takes at least 4 weeks after the beginning of the treatment., 3) When remission of arthritis is sustained, oral prednisolone should be further reduced gradually and finally discontinued [17]. The JCR subsequently issued guidelines in Japan in 2015 (2018 for the English version, and published in 2019), recommending that GC is optional choice and, if used, should only

be used for short periods of time as a bridge therapy [2]. This study found that some cases were treated with GC for a long time, which is speculated to be because some cases of RF − PJIA and OJIA were diagnosed and treated before the publication of the 2007 JCR guidelines, and all cases of RF + JIA were diagnosed and treated before the publication of the 2015 JCR guidelines. The ACR commented on the use of GCs in its 2019 and 2021 guidelines and recommends intra-articular injections when used [18, 19]. Only one patient in this study received intra-articular administration of GC, and this was performed in the USA. All, including this case, received systemic steroids. However, in 2024, there are still a limited number of facilities in Japan that can provide intra-articular injections to children, and the reason why most of the cases did not receive intra-articular injections is that it is assumed that there were even fewer facilities at the time of our cases in this study than there are today.

We have in-house conditions for drug withdrawal of medication, because of the risk of flare after withdrawal of any drug. At our hospital, the conditions for the withdrawal of csDMARDs and bDMARDs are as follows: CRM must be achieved; ID must be maintained for ≥ 12 months; and the patient must request drug withdrawal. We also consider the categories of JIA and the social circumstances of patients. PJIA and RF positivity are considered risk factors for recurrence [8], and social circumstances may be more important for PJIA, which also has a higher age of onset than OJIA. Social circumstances are socially important events, such as entrance exams or the probationary period immediately after employment. In Japan, prolonged absence from work during the probationary period, frequent early leaving and late arrival often has a negative impact on subsequent employment [20]. In case adverse events complicate the continuation of csDMARD administration, we respond by switching to another type of csDMARDs or discontinuing csDMARDs if used in combination with bDMARDs. Fortunately, in the present study, there were no cases of bDMARD discontinuation due to adverse events.

Ebado et al. conducted a questionnaire survey among members of the Paediatric Rheumatology Association of Japan on treatment discontinuation for non-systemic JIA in Japan in 2021. The results of this questionnaire were as follows. Most respondents thought that persistent OJIA was easier to withdraw medication, while extended OJIA and RF + PJIA were more difficult to withdraw, which was one of the important factors in deciding whether to withdraw. Regarding the duration of ID maintenance before starting withdrawal, 43% and 36% of respondents felt that 12–24 months maintenance was necessary for MTX and bDMARDs, respectively, while 42% and 50% felt that more than 24 months maintenance was necessary for MTX and bDMARDs, respectively. In the case of concomitant use of MTX and bDMARDs, 40% decided to withdraw MTX first, 29% decided to withdraw bDMARDs first, and 31% decided to withdraw one after consulting the patient/family. 50% of respondents thought that at least 6 months were required from the start of drug withdrawal to discontinuation. They did not mention withdrawal methods such as immediate discontinuation, dose reduction or prolonging dosing interval [21]. Drug withdrawal at our hospital had been practiced prior to this study and was generally in line with the way drug withdrawal is practiced in Japan.

It has been reported that the flare rate within 12 months after discontinuation of csDMARDs ranges 55.6–78.3%, with extended OJIA and RF + PJIA being more likely to flare [8, 9]. It is well established that most flares occur within 6 months after drug discontinuation [8]. The flare rate after csDMARD withdrawal in our study was similar to that previously reported for RF + PJIA, but lower than that reported for RF − PJIA (i.e., 25%) and OJIA (i.e., 30%). This may be because some cases of RF− PJIA with withdrawal of csDMARDs had concomitant use of bDMARDs, and the majority of OJIA cases in this study were persistent OJIA with low flare rates and only one extended OJIA case with high flare rates. In most cases, as in previous reports, the time to flare after withdrawal of csDMARDs was < 1 year.

A cohort study of patients with PJIA and enthesitis-related arthritis investigated whether the flare rate differed depending on which drug was withdrawn first, namely tumour necrosis factor (TNF) inhibitors or MTX. The flare rate at 12 months after drug withdrawal was 89% in the group in which MTX was withdrawn first and received a TNF inhibitor alone, and 12% in the group in which TNF inhibitors were withdrawn first and received MTX alone [22]. In another report of 220 patients with JIA in whom bDMARDs were discontinued, the rate of re-administration after withdrawal of bDMARDs was 54% (median: 4.7 months), with no significant difference by disease categories. However, the risk of re-admission was reduced in patients who received TCZ and early bDMARD administration, and in those without uveitis complications [23]. In our cases, TCZ was more frequently selected (76%) than TNF inhibitors; thus, a direct comparison with this previous report is not possible. Nevertheless, we have observed cases of PJIA (both RF + /RF −) in which CRM was maintained even with bDMARDs alone; hence, it is possible that csDMARDs can be withdrawn in cases treated with bDMARDs.

On the other hand, bDMARDs were not withdrawn in RF + PJIA, and the flare rate after withdrawal of bDMARDs (after prior csDMARD withdrawal) was very high in patients with RF − PJIA (100%). In RF + PJIA, as

in adult rheumatoid arthritis, the flare rate after drug withdrawal is high and flares can lead to joint destruction. Considering the significant disadvantages associated with withdrawal of bDMARDs, we do not suggest such withdrawal in patients with severe disease. The two patients with RF − PJIA who discontinued treatment with bDMARDs had a sufficient CRM maintenance period prior to withdrawal, but they flared within a year. Therefore, it can be speculated that management without any medication may be difficult in cases of severe RF − PJIA requiring bDMARDs, although the number of our study was small. Meanwhile, in OJIA, one patient with extended OJIA flared after withdrawal of bDMARDs, while one patient with persistent OJIA was previously withdrawn from bDMARDs, then discontinued csDMARDs, and maintained ID for more than 12 months after discontinuation of all medications. Currently (2024), the patient remains on ID. The number of OJIA cases in which bDMARDs was withdrawn was small and can only be speculative, but it suggested that in some cases even OJIA cases that would require bDMARDs could be withdrawn in the persistent OJIA.

Limitations of this investigation included the single-centre, retrospective, and observational nature of the study, the small number of cases, and in particular the few cases of bDMARD withdrawal analysed. Moreover, there are selection biases, such as disease categories (e.g., discontinuation of bDMARDs was not attempted in RF + PJIA).

Although there are a number of limitations, we believe that this study is meaningful because there are few reports on drug withdrawal in Japan, and because there is no consensus on which patients should be withdrawn from medication and what procedures should be used, so accumulating research in this area is desirable. In addition, the types of bDMARDs or csDMARDs that can be administered, and the methods of administration differ between Western countries and Japan (e.g., MTX is often administered orally and bDMARDs are often TCZ intravenous infusion etc.).

Conclusion

The achievement rate of CR for arthritic JIA differed according to the disease category, with OJIA linked to the highest rate. In OJIA, it was possible to discontinue all drugs in some patients with OJIA receiving bDMARDs. In PJIA, patients were able to remain in remission even with bDMARD monotherapy after csDMARD withdrawal; however, withdrawal of bDMARDs was difficult in all two cases. Considering the small number of patients who discontinued treatment with bDMARDs in this study, further investigation regarding drug withdrawal is warranted.

Abbreviations

ABT	Abatacept
ACPA	Anti-cyclic citrullinated peptide antibody
ADA	Adalimumab
ANA	Antinuclear antibody
bDMARDs	Biological disease-modifying antirheumatic drugs
CRM	Clinical remission on medication
CR	Clinical remission off medication
cDMARDs	Conventional synthetic disease-modifying antirheumatic drugs
ERA	Enthesitis-related arthritis
GC	Glucocorticoid
ID	Inactive disease
IFX	Infliximab
JIA	Juvenile idiopathic arthritis
MTX	Methotrexate
NSAIDs	Non-steroidal anti-inflammatory drugs
OJIA	Oligoarticular juvenile idiopathic arthritis
PJIA	Polyarticular juvenile idiopathic arthritis
PsA	Psoriatic arthritis
RF-	Rheumatoid factor-negative
RF+	Rheumatoid factor-positive
TCZ	Tocilizumab

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Authors' contributions

Akira Oshima wrote the paper as first author, contributed to the conception and design of the paper, data acquisition, analysis and interpretation, and gave final approval of the manuscript for publication. Takasuke Ebato, Masanori Kaneko, Yoshiaki Shikama, Tomoyuki Imagawa, made substantial contributions to the conception and design of the article, data acquisition, data analysis and interpretation, provided critical review and guidance to the article, and gave final approval of the manuscript for publication.

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Data availability

The datasets used and/or analysed during the present study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Kanagawa Children's Medical Center (approval number: 145–2).

Consent for publication

Because of the retrospective nature of this study, the Ethics Committee of our institution determined that it was not necessary to obtain written informed consent for this study from the patients/guardians. The documents explaining the study and opt-out documents were available on the website of our institution. No patient offered to decline after the opt-out document was published. This study was conducted in accordance with consensus ethical principles from an appropriate version of the World Medical Association Declaration of Helsinki-Ethical Principles for Medical Research Involving Human Subjects.

Competing interests

Not applicable.

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