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Pediatric Rheumatology (2025) 23:8
https://doi.org/10.1186/s12969-025-01057-8

Pediatric Rheumatology

RESEARCH ARTICLE Open Access

Frequency of remission achievement in the pre-treat-to-target decade in juvenile idiopathic arthritis

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Abstract

Background Over the past two decades there has been a remarkable advance in the management of juvenile idiopathic arthritis (JIA), which has led to considerable improvement in prognosis. In 2018, the introduction of the treat-to-target (T2T) strategy in JIA has been advocated to further ameliorate disease outcome. To provide a benchmark for comparing future outcomes in the "T2T era", this study investigates the percentage of JIA patients who achieved clinical inactive disease (CID) in the decade that preceded the publication of the T2T recommendations in JIA.

Methods The clinical charts of all JIA patients followed at the study center between 2007 and 2017 who were first seen within 6 months after disease onset and had a minimum of 6-month follow-up information available were reviewed retrospectively. The attainment of CID, defined by 2004 Wallace criteria, was assessed cross-sectionally at 6, 12, 24, and 60 months after first observation.

Results A total of 394 patients were included. Patients were classified into four "functional phenotypes": systemic arthritis (7.1%), oligoarthritis (48.2%), polyarthritis (40.4%), and other arthritis (4.3%). The overall frequency of CID was 25.1% at 6 months, 34.5% at 12 months, 44.6% at 24 months, and 49.1% at 60 months. The systemic and oligoarticular subgroups had the highest rates of CID at 6 months (32.1% and 29.5%, respectively) and at 12 months (40% and 41.1%, respectively). At the 60-month evaluation, which was available for 226 out of 394 patients (57.4%), the frequency of CID among patients still followed at study center was 42.9%, 51.7%, 46.7%, and 45.5% for the systemic, oligoarticular, polyarticular, and other arthritis phenotypes, respectively.

Conclusion A sizeable proportion of patients treated in the decade preceding the beginning of the "T2T era" and on continued follow-up did not achieve or maintain the state of CID over the long term. Future studies will determine whether the application of the T2T strategy increases the ability to achieve sustained disease quiescence in patients who respond suboptimally to the conventional therapeutic regimens.

Keywords Juvenile idiopathic arthritis, Treat-to-target, Clinical remission, Inactive disease, Disease outcome

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Introduction

Over the past two decades, the management of juvenile idiopathic arthritis (JIA) has been revolutionized owing to the approval of a growing number of novel and potent therapeutic agents and the shift of treatment strategies toward early aggressive interventions aimed to achieve complete disease control [1]. This advance has improved markedly the long-term outlook of children with JIA [2].

In 2018, the paradigm of explicitly defining a treatment target and applying tight control and necessary therapeutic adjustments to reach the target has been incorporated into treat-to-target (T2T) recommendations for JIA [3]. It has been suggested that transferring this approach into clinical practice will significantly improve the outcomes for patients with JIA [3]. Importantly, one of the main principles included in the recommendations states that the treatment targets and the therapeutic strategy should be based on shared decisions between the parents/patient and the pediatric rheumatology healthcare team.

A recent randomized trial based on the T2T has shown that a sizeable proportion of patients with non-systemic JIA were able to reach drug-free remission after 24 months [4]. A T2T-guided strategy was superior to routine care in reaching clinical remission after 12 months of treatment in patients with polyarticular JIA [5]. Furthermore, the use of anakinra as first-line monotherapy with a T2T approach was found to be highly efficacious in inducing and maintaining inactive disease and in preventing disease- and glucocorticoid-related damage in patients with new-onset systemic JIA [6].

To further evaluate the impact of the application of the T2T strategy in the real word clinical practice, it is important to gain insights into the frequency of complete disease quiescence in children with JIA treated before this approach was proposed. To address this issue, we investigated the rates of clinical inactive disease (CID) achieved during the decade that preceded the publication of the T2T recommendations for JIA [3]. The results of our study provide a measure against which outcomes from other cohorts may be judged and represent a benchmark for future comparisons with the results obtained in the "T2T era".

Methods

Study design and patient selection

In this retrospective observational study patients were included if they: i) had JIA according to the International League of Associations for Rheumatology (ILAR) criteria [7]; ii) were seen at the IRCCS Istituto Giannina Gaslini of Genoa, Italy, within 6 months after disease onset, defined as the time of occurrence of the first symptoms consistent with JIA, between January 2007 and December 2017; and iii) were followed for a minimum of 6 months after baseline visit. Data were also collected, whenever available, at subsequent visits after 12, 24 and 60 months from baseline. For sake of simplicity, patients were grouped into the following four "functional phenotypes": systemic arthritis (including patients with systemic arthritis), oligoarthritis (including patients with persistent oligoarthritis), polyarthritis (including patients with extended oligoarthritis and rheumatoid factor, RF-positive and RF-negative polyarthritis), and other arthritis (including patients with enthesitis-related arthritis, psoriatic arthritis, and undifferentiated arthritis).

The study protocol was approved by the Ethics Committee of Regione Liguria (Genoa, Italy) procedure number 642/2022—DB id 12,828, dated 16 June 2023.

Therapeutic strategy

During the study period, a step-up approach was adopted in most patients. Patients with oligoarthritis were initially treated with intra-articular glucocorticoids (IAGCs) in all affected joints, without a conventional synthetic disease-modifying antirheumatic drug (csDMARD) in case of involvement of one or two large joints, especially the knees, or together with a csDMARD in case of arthritis in three or four joints or involvement of ankle or wrist joints. Treatment of patients with polyarthritis was also usually started by administering IAGCs in all affected joints, always in association with a csDMARD. The exception was represented by patients with diffuse symmetric polyarthritis, especially if RF-positive, or with involvement of cervical spine or hip joints, who were often given a bridging therapy with systemic glucocorticoids (GCs), always in combination with a csDMARD.

If inactive disease was not reached within 3 to 6 months, treatment was escalated by introducing a biologic DMARD (bDMARD), usually a TNF inhibitor, except for patients with oligoarthritis treated only with IAGC, who were first given a csDMARD and, in case of persistent nonresponse, a bDMARD. Patients with ERA and psoriatic arthritis were treated with a similar approach, depending on the severity and extent of joint disease.

IAGC injections were often repeated after a minimum of 4–6 months in patients with arthritis flares. Methotrexate was the preferred csDMARD for oligoarthritis and polyarthritis, while sulfasalazine was favored for enthesitis-related arthritis.Patients with systemic arthritis were given systemic GCs initially, with quick addition of a bDMARD, generally an IL-1 inhibitor, in case of inadequate improvement of flare during tapering or after discontinuation of systemic GCs. However, in the more recent years we started IL-1 inhibition upfront in many patients with systemic JIA, especially those with more prominent extra-articular features and few or no affected

joints. The second-line bDMARD was an alternative IL-1 inhibitor or an IL-6 blocker.

Clinical assessment

The following baseline information was obtained by reviewing clinical charts: sex, age at disease onset and at first visit, ILAR category, and disease duration. Patients were defined as being antinuclear antibody (ANA)-positive if they had at least 2 positive determinations made at least 3 months apart during follow-up, based on indirect immunofluorescence on Hep-2 cells at a titer of ≥ 1:160. Data extracted at each study visit included presence of active systemic manifestations (fever, skin rash, splenomegaly, generalized lymphadenopathy, serositis) and active uveitis (based on the judgement of the ophthalmologist who performed the evaluation), physician's global assessment of overall disease activity (PhGA) on a 21-numbered circle visual analog scale (VAS, where 0 = no activity and 10 = maximum activity) [8], and active joint count (AJC), assessed in 73 joints [9]. A joint was defined as active if it displayed swelling or, in the absence of clinically detectable swelling, pain on motion/tenderness and limited range of motion. Laboratory indicators of inflammation included erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). The medications received by the patients between each study visit were recorded. Data were extracted by five pediatric rheumatology trainees (AIRG, SO, FR, EA and VN) under the supervision of the senior investigator (AR).

Assessment of inactive disease

The state of CID was defined according to the 2004 Wallace criteria [10], as no joint with active arthritis, no systemic manifestations attributable to JIA, no active uveitis, normal acute-phase reactants, and PhGA indicating no disease activity (defined as score of 0 on the 0–10 VAS). However, for a number of patients the full set of Wallace criteria could not be applied due to the lack of the PhGA. For visits where this parameter was not available, but all the other Wallace criteria were met, the absence of disease activity was inferred, as done in previous studies [11, 12], through the review of the patient chart by consensus of two investigators (AIRG and VN). To substantiate this judgement, the caring physician who originally examined the patient at the time of the visit was asked to review independently his/her clinical notes and confirm the state of inactive disease. Any disagreement between the investigators and the caring physician was resolved by consensus with a senior author (AR).

Statistical analysis

Descriptive statistics were reported as medians with first and third quartiles (1st–3rd q) for quantitative variables or as absolute frequencies and percentages for categorical variables. Comparison of continuous variables between two groups of patients was made by means of the Mann–Whitney U test. Categorical data were compared by means of the chi-square test or Fisher's exact test in case of expected frequencies < 5. The Bonferroni adjustment was applied as a correction for multiple comparisons to explore post hoc differences between pairs of patient groups. As the aim was not to compare the frequency of CID and therapeutic interventions across functional phenotypes and because the differences could be easily captured visually, these figures were interpreted only qualitatively.

The software Stata 11 (Stata, College Station, Texas, USA) was used for all statistical analyses.

Results

Out of a total of 1100 patients followed at the study center during the study period, 394 met the inclusion criteria for the present study. The leading reasons for patient exclusion were the first observation made before 2007 or more than 6 months after disease onset, or the lack of the 6-month follow-up visit.The baseline demographic and clinical features of the 394 study patients, considered as a whole and divided by functional phenotype, are presented in Table 1. The main characteristics of these patients were comparable to those of the 706 patients excluded (results not shown).

Overall, the study cohort was characterized by predominance of females, young age at disease onset, high proportion of oligoarthritis, and high frequency of positive ANA status. As highlighted previously, this observation reflects the high prevalence in Italy of the JIA subset possessing these features [13, 14].

Figures 1, 2, 3 and 4 depict the cumulative frequency of the main therapeutic interventions (intra-articular glucocorticoids, IAGCs, systemic GCs, conventional synthetic disease modifying anti-rheumatic drugs, csDMARDs, and biologic DMARDs, bDMARDs) performed over the 5-year study periods (from baseline to 6 months, Fig. 1; from baseline to 12 months, Fig. 2; from baseline to 24 months, Fig. 3; and from baseline to 60 months, Fig. 4).

As expected, systemic GCs were more frequently prescribed in patients with systemic arthritis and only in a minority of those with oligoarthritis; around one-third of patients with polyarthritis or other arthritis received these medications in the first 5 years. In the earlier disease stages, IAGCs were less commonly administered in systemic arthritis than in the other phenotypes. However, the frequency of this therapeutic procedures in systemic arthritis increased to 67% at 5 years, likely reflecting the tendency of many patients to experience a prominence

Table 1 Baseline features of the 394 study patients considered as a whole and divided by functional category

	All patients (*n* = 394)	Systemic arthritis[a] (*n* = 28)	Oligoarthritis (*n* = 190)	Polyarthritis[b] (*n* = 159)	Other arthritis[c] (*n* = 17)
N (%) females	292 (74.1)	16 (57.1)	137 (72.1)	126 (79.2)	13 (76.5)
Age at disease onset, years	3 (1.8—6.9)	5.2 (2.9—8.9)	2.7 (1.8—5.9)	2.8 (1.9—6.8)	6 (1.3—11.7)
Age, years	3.2 (2—7)	5.3 (3.2—8.9)	3 (2—6.1)	3.1 (2—6.9)	6.1 (1.6—12.6)
Disease duration, months	2.1 (1.1 – 3.7)	1.34 (0.7 – 2.2)	2.2 (1.1 – 4.2)	2.0 (1.1–3.4)	2.06 (1.6 –4.0)
N (%) ANA-positive	271/392 (69.1)	6 (22.2)	151 (79.9)	105 (65.4)	10 (58.8)
N (%) with uveitis	16/375 (4.3)	0 (0)	9 (4.7)	7 (4.4)	0 (0)
Physician global assessment	4 (3—6)	5 (2.8—6.2)	3 (2—4)	6 (4 –7)	3 (2—5)
Count of active joints	2 (1—5)	1.5 (0—5.8)	2 (1—2)	5 (3 –7)	2 (1—4)
Erythrocyte sedimentation rate, mm/h	34 (16 – 51)	44 (29.5—67)	31 (14—46.3)	36.5 (17 –54)	38 (9.3—63)
C-reactive protein, mg/dl	0.8 (0.5—2.3)	6.6 (1.3—11.6)	0.5 (0.5 –1.3)	1.03 (0.5 – 2.5)	0.7 (0.5 –2.7)

Data are the median (1st- 3rd quartile), unless otherwise indicated

[a] 20 with active systemic manifestations (19 fever, 18 rash, 3 hepatosplenomegaly, 6 generalized lymphadenopathy)

[b] 53 with extended oligoarthritis, 95 with rheumatoid factor-negative polyarthritis, 11 with rheumatoid factor-positive polyarthritis

[c] 4 with enthesitis-related arthritis, 5 psoriatic arthritis, 8 with undifferentiated arthritis

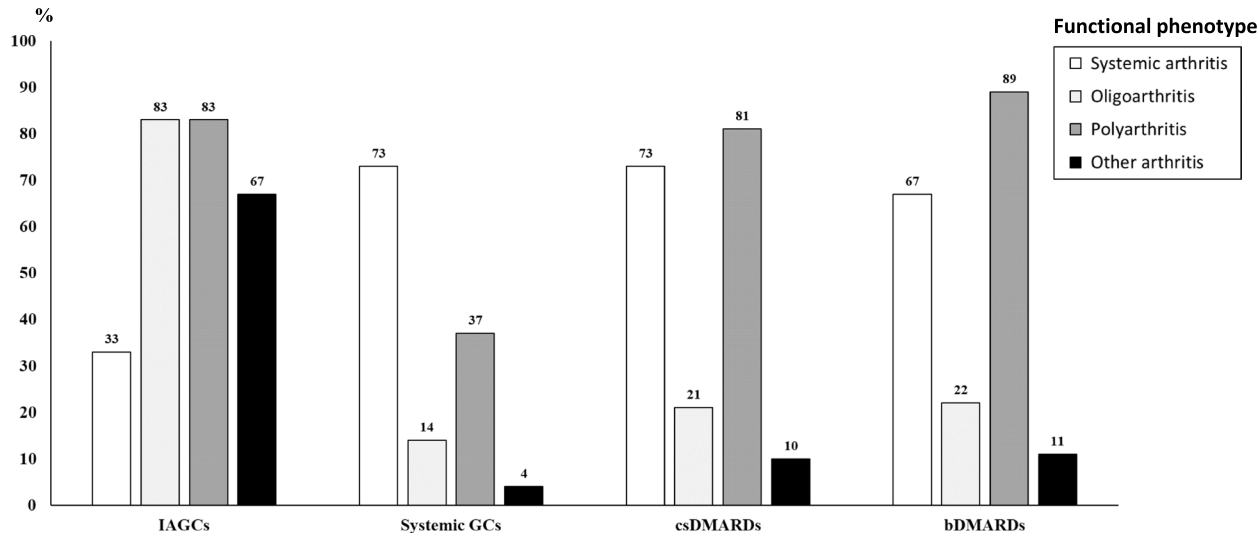

Fig. 1 Cumulative frequency of the main therapeutic interventions in the four disease phenotypes from baseline to 6 months. IAGCs = intra-articular glucocorticoids; GCs = glucocorticoids; csDMARDs = conventional systemic disease modifying anti-rheumatic drugs; bDMARDs = biologic DMARDs

of arthritis over extra-articular symptoms in the more advanced disease stages.

Around two-thirds of the patients with oligoarthritis, polyarthritis and other arthritis were given IACGs within the first 6 months. This observation is in line with our strategy to initially inject all affected joints in children with these disease phenotypes, excluding those with extensive symmetric polyarthritis or involvement of cervical spine or hips, which are usually candidates for systemic GCs. Overall, more than 65% of patients across all phenotypes underwent one or more IAGC procedures over the 5-year study period.

The vast majority of patients with polyarthritis and, to a lesser extent, other arthritis were prescribed csDMARDs in the first 6 months, whereas only 21% of the patients with oligoarthritis, respectively, received these agents in the earlier disease stages. The frequency of utilization of csDMARDs increased steadily along the study period, so that at 5 years nearly all patients with polyarthritis and other arthritis, and 83% and 29% of

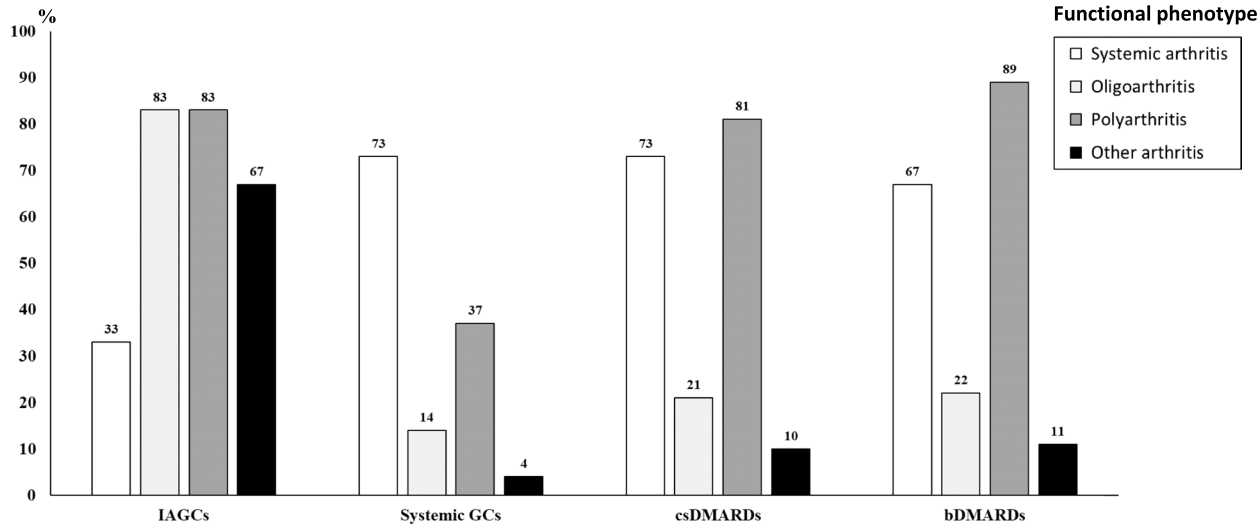

Fig. 2 Cumulative frequency of the main therapeutic interventions in the four disease phenotypes from baseline to 12 months. IAGCs = intra-articular glucocorticoids; GCs = glucocorticoids; csDMARDs = conventional systemic disease modifying anti-rheumatic drugs; bDMARDs = biologic DMARDs

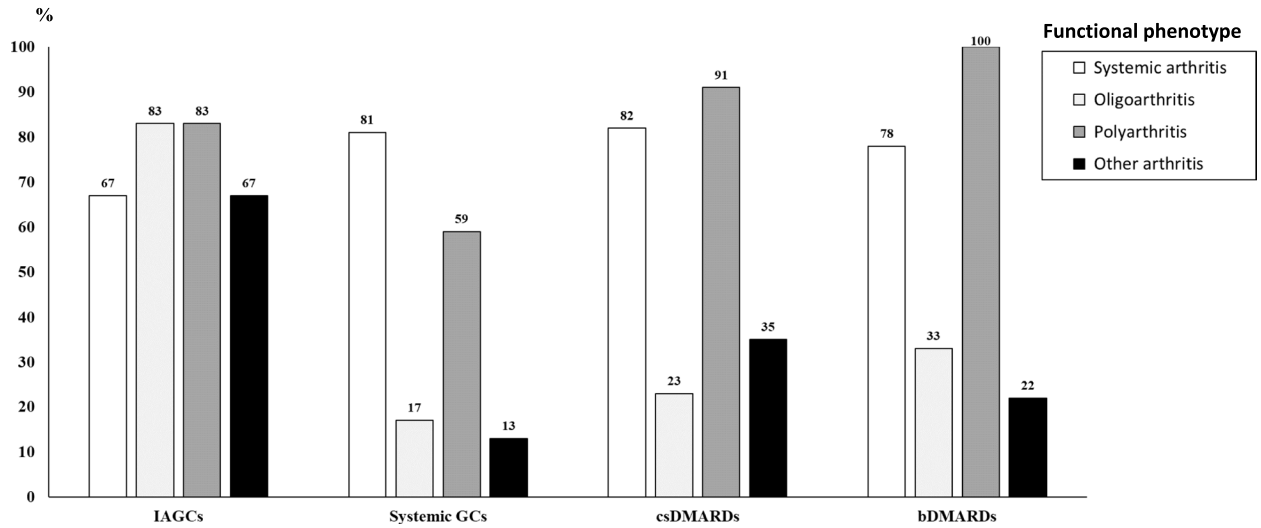

Fig. 3 Cumulative frequency of the main therapeutic interventions in the four disease phenotypes from baseline to 24 months. IAGCs = intra-articular glucocorticoids; GCs = glucocorticoids; csDMARDs = conventional systemic disease modifying anti-rheumatic drugs; bDMARDs = biologic DMARDs

the patients with systemic arthritis and oligoarthritis, respectively, had taken these medications.

In the first 6 months, bDMARDs were given to 67% of the patients with systemic arthritis and in very few patients with the other phenotypes. Like for csDMARDs, the use of these agents increased progressively from baseline to 5 years, particularly in systemic arthritis and, to a lesser extent, in polyarthritis and other arthritis. At five years, only 33% of the patients with oligoarthritis received bDMARDs.

The frequency of CID in the four functional phenotypes, assessed cross-sectionally at each study visit, is presented in Fig. 5. At 6 and 12 months more patients with systemic arthritis and oligoarthritis had achieved CID, whereas the proportion of CID was comparable

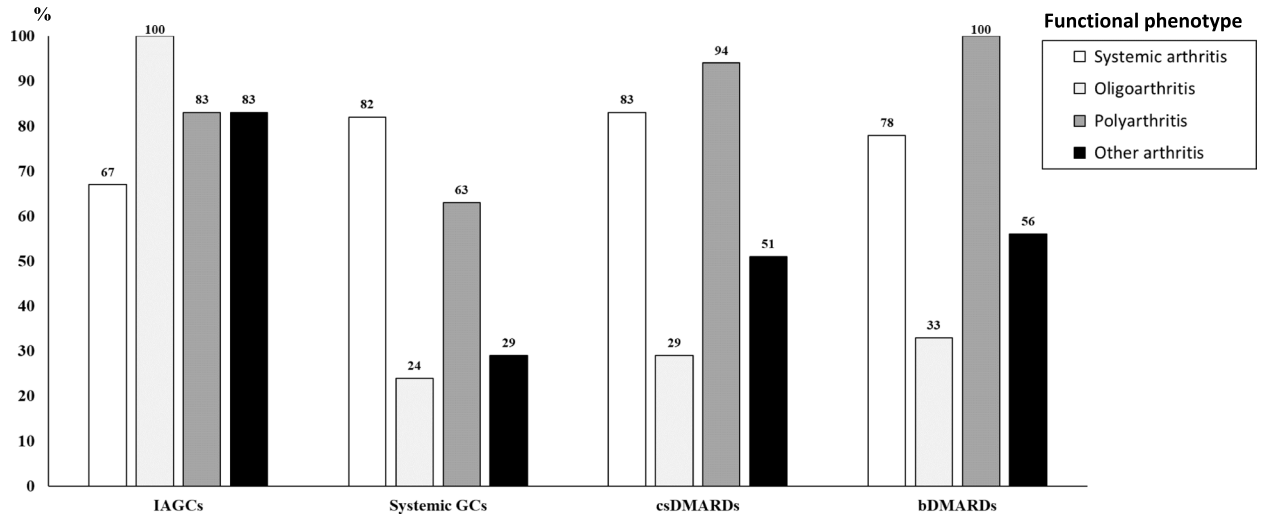

Fig. 4 Cumulative frequency of the main therapeutic interventions in the four disease phenotypes from baseline to 60 months. IAGCs = intra-articular glucocorticoids; GCs = glucocorticoids; csDMARDs = conventional systemic disease modifying anti-rheumatic drugs; bDMARDs = biologic DMARDs

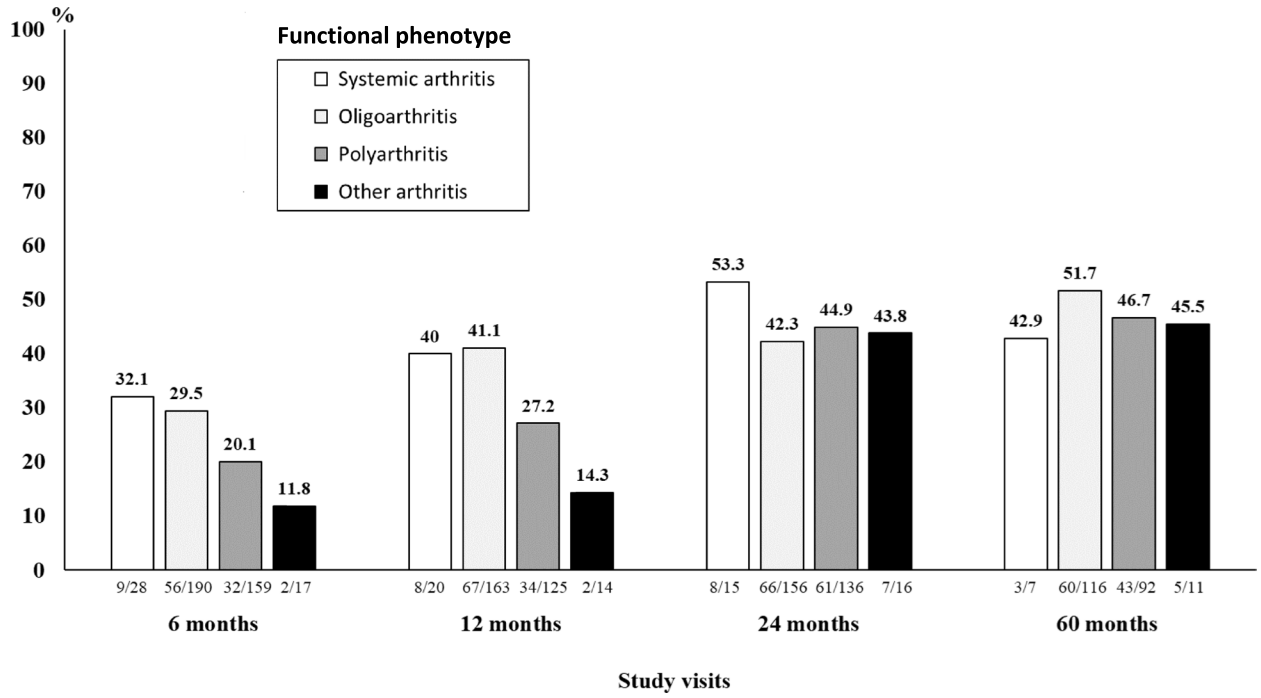

Fig. 5 Frequency of clinical inactive disease assessed cross-sectionally at each study visit in the four disease phenotypes from baseline to 60 months

across disease phenotypes at 2 and 5 years. Overall, 40 to 50% of the patients in each group reached CID at 5 years, with the frequency of achievement of such state in patients seen at 2 years and still followed at 5 years remaining overall stable.

Discussion

Our study documents the frequency of achievement of CID among patients followed in routine clinical practice in the decade preceding the publication of the recommendations for the T2T in JIA [3]. The inclusion of the sole patients who were first seen at our center within 6

months after disease onset and were followed by us until the last follow-up visit after 5 years ensures that the therapeutic management was uniform throughout the entire disease course. Because our hospital is a referral facility for pediatric rheumatic diseases for the entire country, we receive many patients from other centers who have already been managed using various therapeutic interventions, often to seek a second opinion. Because the treatments administered to these patients are often different than those used by us, we thought that their inclusion could alter the homogeneity of treatment regimens administered.

During the study period, we adopted in most patients a step-up approach, aiming for complete suppression of inflammatory activity as early as possible. Treatment was conducted through a conventional regimen, tailored on the disease activity and severity, and escalated in case the therapeutic goal was not reached at follow-up evaluations. We found that 40 to 50% of the patients treated with such approach, which was not yet based on a strict T2T, had reached the state of CID at 2 years after treatment initiation and that the percentage remained overall stable after 5 years.

It should be considered that the figures for CID at 5 years are likely underestimated, as 30% of the 323 patients who had a follow-up visit at 2 years did not have a 5-year evaluation. It is conceivable that a sizeable proportion of these patients was lost of follow-up because of persistent disease quiescence. Nonetheless, the proportion of patients with persistently active disease at last evaluation remain substantial.

The frequency of CID observed in our study falls within the range reported in long-term analyses of other JIA cohorts seen during the same study period, which varies from 21 to 75% [15–20]. The disparities in the figures across studies may depend on differences in the study design, method used to define inactive disease, therapeutic regimens adopted, or patient characteristics. Nevertheless, altogether these data indicate that a consistent proportion of children with JIA treated in the decade preceding the T2T era, when many of the contemporary bDMARDs were already available, were unable to reach or maintain the state of inactive.

A number of caveats should be considered when interpreting our findings. The study design was retrospective, which implies the risk of missing or possibly erroneous data. Our results reflect a single-center experience, which means that they may not be generalized to series followed in other settings. The small size of some disease categories precludes drawing reliable conclusions about their likelihood to attain CID. Due to the nonrandomized and observational nature of our analysis, we cannot exclude that patient who achieved CID might have had a less aggressive disease than those who did not. As noted above, the meaning of the long-term CID figures may be limited by the high proportion missing the 5-year evaluation. For the same reason, we could not establish the proportion of patients who had reached CID without medications over the long term. In a number of patients the state of CID could not be formally established according to Wallace criteria, owing to the lack of the PhGA, but was inferred through the review of clinical charts. We recognize that the missing data for the PhGA might have biased our results. Furthermore, we could not provide the figures for an alternative method of assessing CID based on the Juvenile Arthritis Disease Activity Score (JADAS) due to the lack of the patient's/parent's assessment of the overall wellbeing in a sizeable proportion of patients. The lack of inclusion of patients diagnosed after 6 months from disease onset may not reflect the real world experience and might have led to observe a higher rate of CID.

Conclusions

In summary, a sizeable proportion of our JIA patients treated in the decade preceding the introduction of the T2T strategy (2007–2017) did not reach or maintain the state of CID over the long-term. This finding contrasts with our previous observation of remarkable improvement in terms of physical disability, disease damage and health-related quality of life (HRQL) among patients followed in the same epoch as compared to those seen before the 2000s [2, 13]. Future experiences on the application of the T2T strategy will determine whether this approach increases the ability to achieve sustained disease quiescence in patients who respond suboptimally to the conventional therapeutic protocols. The research agenda also calls for the design of innovative clinical trials to deliver precision medicine, the discovery of biomarkers that can predict response to treatments, disease progression and disease flare after treatment withdrawal, and the continued development of therapies and therapeutic strategies for patients with treatment-refractory disease.

Abbreviations

AJC	Active joint count
ANA	Antinuclear antibody
bDMARDs	Conventional synthetic disease-modifying antirheumatic drugs
CID	Clinical inactive disease
CRP	C-reactive protein
csDMARDs	Conventional synthetic disease-modifying antirheumatic drugs
ESR	Erythrocyte sedimentation rate
GCs	Glucocorticoids
HRQL	Health-related quality of life
IAGCs	Intra-articular glucocorticoids
JIA	Juvenile idiopathic arthritis
NSAIDs	Non-steroidal anti-inflammatory drugs
PhGA	Physician global assessment
RF	Rheumatoid factor
T2T	Treat-to-target
VAS	Visual analogue scale

Acknowledgements
Ana Isabel Rebollo-Giménez has held a fellowship supported by the Sociedad Española de Reumatología.

Authors' contributions
All authors participated in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Study conception and design: AIRG, EN, SR, MB, RN, AC, AR. Acquisition of data: AIRG, SO, FR, EA, VN. Analysis and interpretation of data: AIRG, AP, LC, AR. Statistical Analysis: AIRG, AP.

Funding
The authors have received no financial support for the research, authorship and/or publication of this article.

Data availability
Additional data are available upon request from the corresponding author. Dr. Rebollo-Giménez had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Declarations

Ethics approval and consent to participate
The study protocol was approved by the Ethics Committee of Regione Liguria (Genoa, Italy) under protocol number 642/2022—DB id 12828, dated 16 June 2023.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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Received: 4 March 2024 Accepted: 27 December 2024
Published online: 23 January 2025

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