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BRIEF REPORT

Long-Term Maintenance of Clinical Responses by Individual Patients With Polyarticular-Course Juvenile Idiopathic Arthritis Treated With Abatacept

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Objective. To investigate the frequency and trajectories of individual patients with polyarticular-course juvenile idiopathic arthritis (JIA) achieving novel composite end points on abatacept.

Methods. Data from a clinical trial of subcutaneous abatacept (NCT01844518) and a post hoc analysis of intravenous abatacept (NCT00095173) in patients with polyarticular-course JIA were included. Three end points were defined and evaluated: combined occurrence of low disease activity (LDA) measured by the Juvenile Arthritis Disease Activity Score; 50% improvement in American College of Rheumatology criteria for JIA (ACR50); and patient-reported outcomes. Patient-reported outcomes included visual analog scale score of minimal pain (pain-min) and Childhood Health Assessment Questionnaire disability index score of 0 (C-HAQ DI0). In this post hoc analysis, maintenance of month 13 and 21 end points (LDA+pain-min, LDA+C-HAQ DI0, and ACR50+pain-min) in those who achieved them at month 4 was determined.

Results. Composite end points (LDA+pain-min, LDA+C-HAQ DI0, and ACR50+pain-min) were achieved at month 4 (44.7%, 19.6%, and 58.9% of the 219 patients treated with subcutaneous abatacept, respectively). Of those who achieved LDA+pain-min at month 4, 84.7% (83 of 98) and 65.3% (64 of 98) maintained LDA+pain-min at months 13 and 21, respectively. The proportions of patients meeting LDA+pain-min outcomes increased from 44.7% (98 of 219) at month 4 to 54.8% (120 of 219) at month 21. The frequency of patients who met an LDA+C-HAQ DI score of 0 increased from 19.6% (43 of 219) at month 4 to 28.8% (63 of 219) at month 21.

Conclusion. Among individual patients with polyarticular-course JIA treated with abatacept who achieved 1 of the combined clinical and patient-reported outcomes composite end points, many maintained them over 21 months of abatacept treatment.

INTRODUCTION

Juvenile idiopathic arthritis (JIA) is the term used to describe a group of noninfectious inflammatory conditions of unknown etiology with onset prior to age 16 years resulting in chronic arthritis for a minimum duration of 6 weeks (1,2). JIA may be associated with extraarticular features such as uveitis, fever, and rashes (1,2). Children and adolescents with JIA often experience

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SIGNIFICANCE & INNOVATIONS

- The analysis of data from a phase 3 multicenter study and a post hoc analysis confirms that individual children age 2–17 years with polyarticular-course juvenile idiopathic arthritis (JIA) treated with subcutaneous (SC) or intravenous (IV) abatacept achieved composite end points comprised of both a clinically meaningful end point and a meaningful patient-reported outcome end point.
- Moreover, individual children with polyarticular-course JIA treated with SC or IV abatacept who achieved novel composite end points can maintain or further improve these responses/end points over 21 months.

poor health-related quality of life and carry the risk of permanent joint damage, especially if joint inflammation remains poorly treated (1,2). Abatacept selectively modulates T-cell costimulation and has been found to be effective and well tolerated in patients with polyarticular-course JIA when administered by the intravenous (IV) or subcutaneous (SC) route (3,4). We have previously shown that the clinical benefits in patients with polyarticular-course JIA can be maintained for 7 years with IV abatacept treatment (5) and for over 24 months with SC abatacept (3). A preliminary assessment of patients with polyarticular-course JIA treated with SC abatacept examined the maintenance of clinical response over 2 years and treatment response by individual patients and noted that the majority achieved and maintained efficacy end points over time (6). Treatment with IV or SC abatacept has also led to substantial improvements in patient-reported outcomes, such as chronic pain and functional ability (3,5).

In recent years, treat-to-target strategies have been recommended for the treatment of polyarticular-course JIA (7). In support of implementing treat-to-target therapeutic strategies, clinicians could benefit from information pertaining to the persistence of treatment responses in individual patients. The results of a recent study that evaluated disease activity and patient-reported outcomes in the same patients with polyarticular-course JIA using machine learning suggested that both clinical and patient-reported outcomes show similar trajectories over time.

The main goals of this post hoc analysis were to investigate the frequency and trajectories of achieving treatment goals in individual patients with polyarticular-course JIA, as well as the simultaneous achievement of low disease activity (LDA) in combination with highly favorable patient-reported outcomes in response to SC abatacept treatment and subsequent maintenance for up to 21 months.

PATIENTS AND METHODS

Compliance with research ethics standards. Studies included in this post hoc analysis were conducted in accordance with the Declaration of Helsinki, the International Conference on Harmonization Guidelines for Good Clinical Practice, and local regulations. At each site, an individual institutional review board or independent ethics committee approved the protocol, consent forms, and any other written information provided to patients or their legal representatives. Written consent was obtained from all participants.

Data sets and study details. Data presented are from analyses of 2 abatacept studies (3,4). First, data from a post hoc analysis of a 24-month, single-arm, open-label, multicenter phase 3 trial of weekly weight-tiered SC abatacept in patients with polyarticular-course JIA who had an inadequate response/intolerance to ≥1 disease-modifying antirheumatic drug (NCT01844518) (3). Second, additional data were included from a previous post hoc analysis of a double-blind, randomized, placebo-controlled withdrawal trial of IV abatacept in patients with JIA age 6–17 years (NCT00095173) (4). Patients who failed to achieve an improvement of 30% in American College of Rheumatology criteria for JIA (ACR30) were discontinued from the study. All patients remaining after month 4 continued abatacept treatment.

In both abatacept studies, 6 ACR JIA criteria core set variables were measured: number of active joints; number of joints with limitation of motion; physician's global assessment of disease activity measured using a visual analog scale (VAS); parent's global assessment of patient overall well-being measured using a VAS; cross-culturally adapted and validated versions of the Childhood Health Assessment Questionnaire disability index (C-HAQ DI) (8); and a laboratory marker of inflammation (either C-reactive protein [CRP] or erythrocyte sedimentation rate). The C-HAQ DI measures physical function limitations on a scale of 0–3 across 8 domains of disability components, with higher values indicating greater disability.

Composite end points. In this analysis, we aimed to assess the ability of individual patients to simultaneously achieve both a clinical efficacy end point and a patient-reported outcome end point over time. While clinical end points such as the Juvenile Arthritis Disease Activity Score in 27 joints (JADAS-27) are valuable, it is also important to assess meaningful improvements in patient-reported outcomes for each child. However, the evaluated values of pain (measured on a 0–100 mm VAS [pain-VAS], with higher values indicating greater pain) and C-HAQ DI scores are not included in the JADAS-27 score, and although the ACR JIA criteria response measures include the C-HAQ DI score, they do not include a pain-VAS. To assess a patient-reported outcome variable independent of the efficacy variable, the patient-reported outcomes evaluated here included pain, as reduction in pain is a priority for patients with polyarticular-course JIA (9), along with components of the ACR JIA criteria core set variables (3). Therefore, combined clinical and patient-reported outcome composite end points were devised for this study, and the following

3 composite end points were then evaluated in individual patients: LDA (defined as a JADAS-27 score using a CRP level of ≤3.8) (10–12) plus minimal pain (LDA+pain-min); LDA plus absence of disability (LDA + a C-HAQ DI score of 0 [C-HAQ DI0]); and a 50% improvement from baseline to month 4 in ACR JIA criteria (ACR50) plus minimal pain (ACR50+pain-min).

Definitions of favorable clinical and patient-reported outcomes considered in composite end points. Favorable patient-reported outcomes were defined as the absence of disability measured by the C-HAQ DI0 and no more than minimal chronic pain (a pain-VAS score of <35 mm) (13). Favorable clinical outcomes considered were LDA and ACR50 (8).

Statistical analyses. Data were analyzed using SAS, version 9.4. Descriptive statistics and Kaplan-Meier analyses were performed to determine the proportion of patients achieving composite end points (LDA+pain-min, LDA+C-HAQ DI0, and ACR50+pain-min) at month 4 (selected as a time point to match the follow-up time for the primary end point of the SC abatacept study [NCT01844518]) and the maintenance of these responses at months 13 and 21 (7 and 26 for IV). Months 13 and 21 were the closest time points to year 1 and year 2 milestones where data were collected, respectively (some month 24 efficacy data were inadvertently not collected by investigators at some sites).

The proportions of patients achieving responses were assessed in the intent-to-treat (ITT) population, defined as all treated patients (patients with missing data were imputed as nonresponders). For the continuous patient-reported outcome variables, an "as observed" (missing values were not imputed) analysis was conducted.

Heat maps and Sankey diagrams were used to evaluate individual patients as either composite end point responders or nonresponders over the course of study. Patients with missing values (including patients who discontinued due to lack of efficacy) were considered as nonresponders for the ACR50+pain-min end point. Bar graphs were used to summarize proportions of patients meeting composite end points at month 4 and continuing to meet these end points at months 13 and 21. Time-to-achieve composite end points are shown using Kaplan-Meier plots. We also evaluated the proportion of patients who achieved ACR50+pain-min with LDA+pain-min and LDA+C-HAQ DI0 end points. The results presented in this study are for the overall population of the SC abatacept study (combining the 2 age cohorts). Results for the individual cohorts from the SC abatacept study (cohort 1, patients age 6–17 years and cohort 2, patients age 2–5 years) and IV study are reported in Supplementary Figure 1, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.25156.

RESULTS

Patients and clinical response. Baseline characteristics of patients in the SC and IV abatacept trials included in this analysis are shown in Table 1 and Supplementary Table 1, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.25156. Before or by month 4, 7 of the 219 patients (3.2%) discontinued from the study due to lack of efficacy with open-label SC abatacept treatment. By month 4, LDA was achieved by 46.1% (101 of 219) of patients, and an ACR50 response was achieved by 57.1% (165 of 219).

Composite end points in overall study population. Figure 1A shows the proportion of patients treated with SC abatacept who achieved composite end points at month 4 and continued to meet these same end points at months 13 and 21. Of the 44.7% (98 of 219) who achieved LDA+pain-min at month 4, 84.7% (83 of 98) maintained this status at month 13, and 65.3% (64 of 98) maintained this at month 21. Of the 58.9% (129 of 219) who achieved ACR50+pain-min at month 4, 84.5% (109 of 129) maintained this at month 13, and 73.6% (95 of 129) maintained this at month 21. Supplementary Figure 2, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.25156, shows comparable analyses of data from the phase 3 trial of IV abatacept. In data from this trial, 24.7% (47 of 190) of patients achieved LDA+pain-min at month 4; 66.0% (31 of 47) maintained this status at month 7, and 48.9% (23 of 47) maintained it at month 26. Similar to the SC trial, lower proportions of patients achieved LDA+C-HAQ DI0 at month 4 (data not shown).

Figure 1B shows time to achievement of all 3 composite end points in patients treated with SC abatacept. There are marked differences in the median time to achieving composite end points ranging from 1.9 (ACR50+pain-min) to 21.5 months (LDA+C-HAQ DI0).

Composite end points in individual patients. Figure 2 shows 3 heat maps displaying the individual responder status over time for all patients treated with SC abatacept who met composite end points at month 4. Overall, the majority of patients who achieved LDA+pain-min (Figure 2A), LDA+C-HAQ DI0 (Figure 2B), and ACR50+pain-min (Figure 2C) at month 4 maintained this status at month 13 (87.8%, 84.0%, and 81.4%, respectively) and month 21 (72.4%, 72.0%, and 60.5%, respectively).

The Sankey diagrams shown in Supplementary Figure 3, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.25156, provide a summation of the course of individual patients treated with SC abatacept meeting composite end points. The proportion of patients achieving LDA+pain-min increased from 44.7% (98 of 219) at month 4 to 54.8% (120 of 219) at month 21. Patients who were

Table 1. Baseline demographic and disease characteristics in the subcutaneous abatacept trial*

Characteristic	Cohort 1 (6–17 years) (n = 173)	Cohort 2 (2–5 years) (n = 46)	Overall population (n = 219)
Age, median (IQR) years	13.0 (10.0–15.0)	4.0 (3.0–5.0)	11.0 (2.0–17.0)†
Female	136 (78.6)	28 (60.9)	164 (74.9)
Weight, median (IQR) kg	45.0 (31.5–57.0)	18.0 (15.0–21.1)	37.4 (12.0–146.3)†
Weight categories, kg			
<25	18 (10.4)	43 (93.5)	61 (27.9)
25 to <50	74 (42.8)	3 (6.5)	77 (35.2)
≥50	81 (46.8)	0	81 (37.0)
Race‡			
White	144 (83.2)	44 (95.7)	188 (85.8)
Black/African American	14 (8.1)	1 (2.2)	15 (6.8)
Other	15 (8.7)	1 (2.2)	16 (7.3)
Disease duration, median (IQR) years	2.0 (0.0–4.0)	0.5 (0.0–1.0)	1.0 (0–15)†
<2	102 (59.0)	42 (91.3)	144 (65.8)
2 to <5	37 (21.4)	4 (8.7)	41 (18.7)
5 to ≤10	30 (17.3)	0	30 (13.7)
>10	4 (2.3)	0	4 (1.8)
JIA categories			
Polyarthritis RF negative	94 (54.3)	29 (63.0)	123 (56.2)
Polyarthritis RF positive	46 (26.6)	3 (6.5)	49 (22.4)
Extended oligoarthritis	19 (11.0)	10 (21.7)	29 (13.2)
Systemic arthritis	5 (2.9)	0	5 (2.3)
Psoriatic arthritis	0	4 (8.7)	4 (1.8)
Enthesitis-related arthritis	4 (2.3)	0	4 (1.8)
Undifferentiated or persistent oligoarthritis§	5 (2.9)	0	5 (2.3)
JIA-ACR core set variables			
No. of active joints, median (IQR)	10.0 (6.0–19.0)	7.0 (6.0–12.0)	9.0 (6–17)
No. of joints with LOM, median (IQR)	8.0 (4.0–15.0)	8.0 (4.0–11.0)	8 (4–14)
PhGA median (IQR) mm	48.0 (31.0–67.0)	50.0 (3.50–6.00)	48 (32.0–65.0)
P-well VAS score, median (IQR) mm	47.8 (24.1–68.0)¶	42.1 (17.9–54.7)	47.2 (21.8–65.6)
C-HAQ DI, median (IQR)	0.9 (0.4–1.5)¶	1.2 (0.8–1.6)	1.0 (0.5–1.6)
CRP, median (IQR) mg/dl#	0.2 (0.1–0.9)	0.1 (0.1–1.4)	0.2 (0.1–1.0)
JADAS-27 CRP, median	19.1¶	16.1	18.1
JADAS-71 CRP, median (IQR)	21.0 (13.5–30.3)**	18.1 (14.0–23.1)	19.9 (13.8–28.1)
Pain VAS score, median, mm	49	39.5	–
Methotrexate use at baseline	136 (78.6)	37 (80.4)	173 (79.0)
Methotrexate dose at baseline, median (IQR) mg/m^2/week	11.6 (9.7–14.4)	13.3 (10.9–15.3)	–
Route of methotrexate administration			
Oral	76 (55.9)	18 (48.6)	–
Parenteral††	60 (44.1)	19 (51.4)	–
Oral corticosteroid use at baseline‡‡	56 (32.4)	9 (19.6)	66 (30.1)
Oral prednisone (or equivalent) dose at baseline, median (IQR) mg/kg/day	0.1 (0.1–0.2)§§	0.2 (0.2–0.4)¶¶	–
Prior biologic use##	46 (26.6)	10 (21.7)	56 (25.6)

* Values are the number (%) unless indicated otherwise. ACR = American College of Rheumatology; C-HAQ DI = Childhood Health Assessment Questionnaire disability index; CRP = C-reactive protein; JADAS-27 = Juvenile Arthritis Disease Activity Score in 27 joints; JADAS-71 = Juvenile Arthritis Disease Activity Score in 71 joints; JIA = juvenile idiopathic arthritis; LOM = limitation of motion; PhGA = physician global assessment of disease activity; P-well = parent's global assessment of well-being; RF = rheumatoid factor; VAS = visual analog scale.
† Values are the median (minimum, maximum).
‡ Race and ethnicity were self-reported from a fixed set of categories.
§ Protocol violation.
¶ N = 172.
# Normal range for CRP: ≤0.6 mg/dl.
** N = 171.
†† Includes subcutaneous and intramuscular.
‡‡ Prednisone or prednisolone.
§§ N = 52.
¶¶ N = 8.
Adalimumab, etanercept, and tocilizumab.

LDA+pain-min responders maintained their response over time (see Supplementary Figure 3A). Likewise, the proportion meeting the LDA+C-HAQ DI0 end point increased from 19.6% (43 of 219) at month 4 to 28.8% (63 of 219) at month 21, while only a few patients reaching this composite end point at month 4 lost it later (see Supplementary Figure 3B). Responders for the ACR +pain-min end point increased from 58.9% (129 of 219) at month 4 to 63.5% (139 of 219) at month 21 (see Supplementary

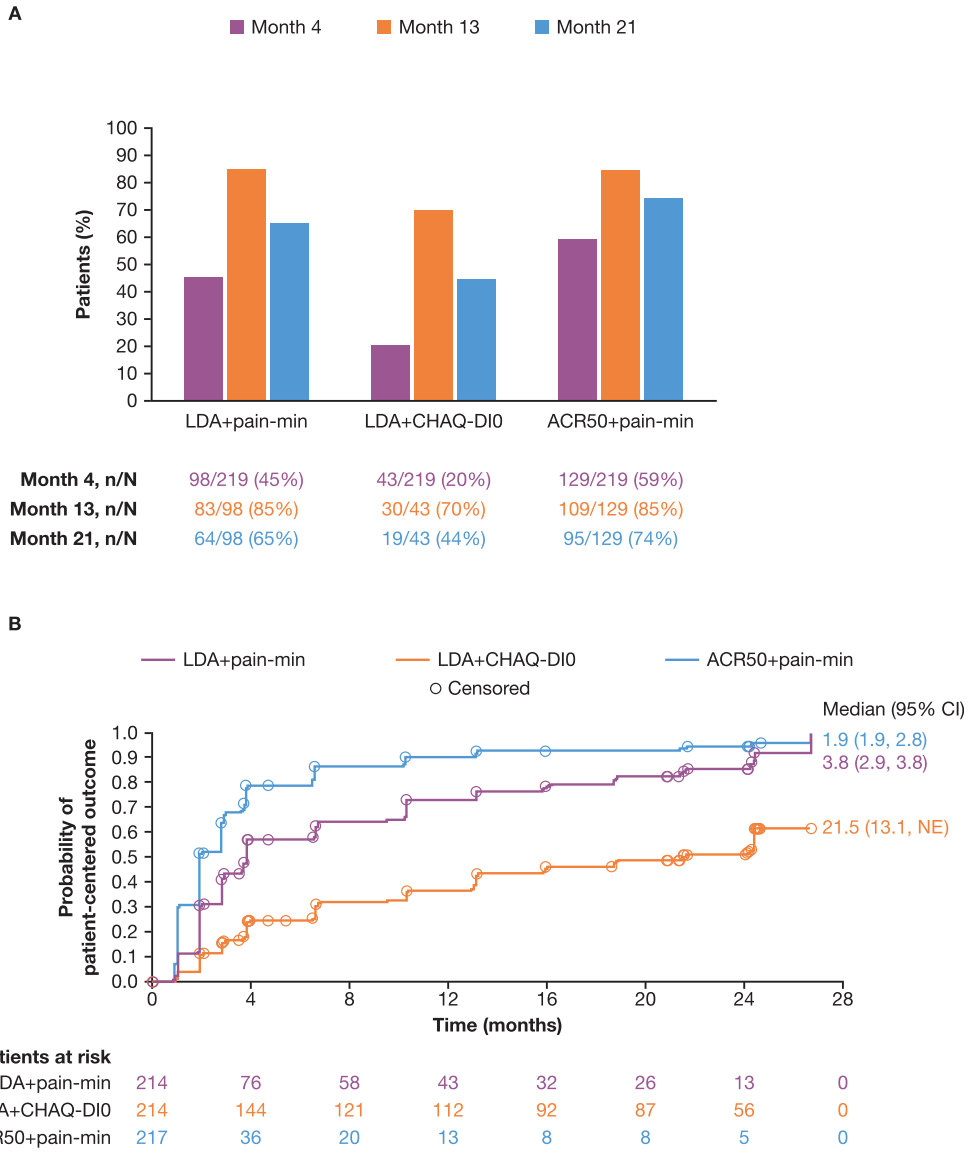

Figure 1. Proportions of patients meeting composite end points at month 4 and maintaining response at months 13 and 21 (**A**) and Kaplan-Meier plots for the time to achievement of composite end points in patients treated with subcutaneous abatacept (**B**). For panel A, the percentage at months 13 and 21 is based on the number of patients who achieved response at month 4 (denominator). For panel B, the month was calculated using the actual days since abatacept treatment/30 and rounded to 1 decimal. Patients without the combined event are censored at the last assessment for the combined event. The number at month 0 is the number of treated patients with the combined event at day 1. Patients who have the event at baseline are excluded from the analysis. 95% CI = 95% confidence interval; ACR50+pain-min = 50% improvement in Juvenile Idiopathic Arthritis–American College of Rheumatology criteria plus minimal pain; LDA = low disease activity; LDA+pain-min = LDA plus minimal pain; LDA+CHAQ-DI0 = LDA plus Childhood Health Assessment Questionnaire disability index score of 0; NE = not evaluable.

Figure 3C). However, achievement of this end point was less well maintained compared with the other composite end points (LDA+pain-min and LDA+C-HAQ DI0).

DISCUSSION

In this post hoc analysis of data from 2 phase 3 multicenter studies of abatacept in patients with polyarticular-course JIA, we explored the achievement of select combined clinical and patient-reported outcome composite end points on treatment initiation. The majority of individual patients who achieved the composite end points at month 4 maintained these responses through month 21. These findings attest to the efficacy of abatacept in patients with polyarticular-course JIA with benefits on several aspects of health-related quality of life, namely patient well-being, pain, and functional ability. Notably, disease flares are a major source of patient concern. Additionally, disease worsening may adversely impact a patient's family (14). The findings from

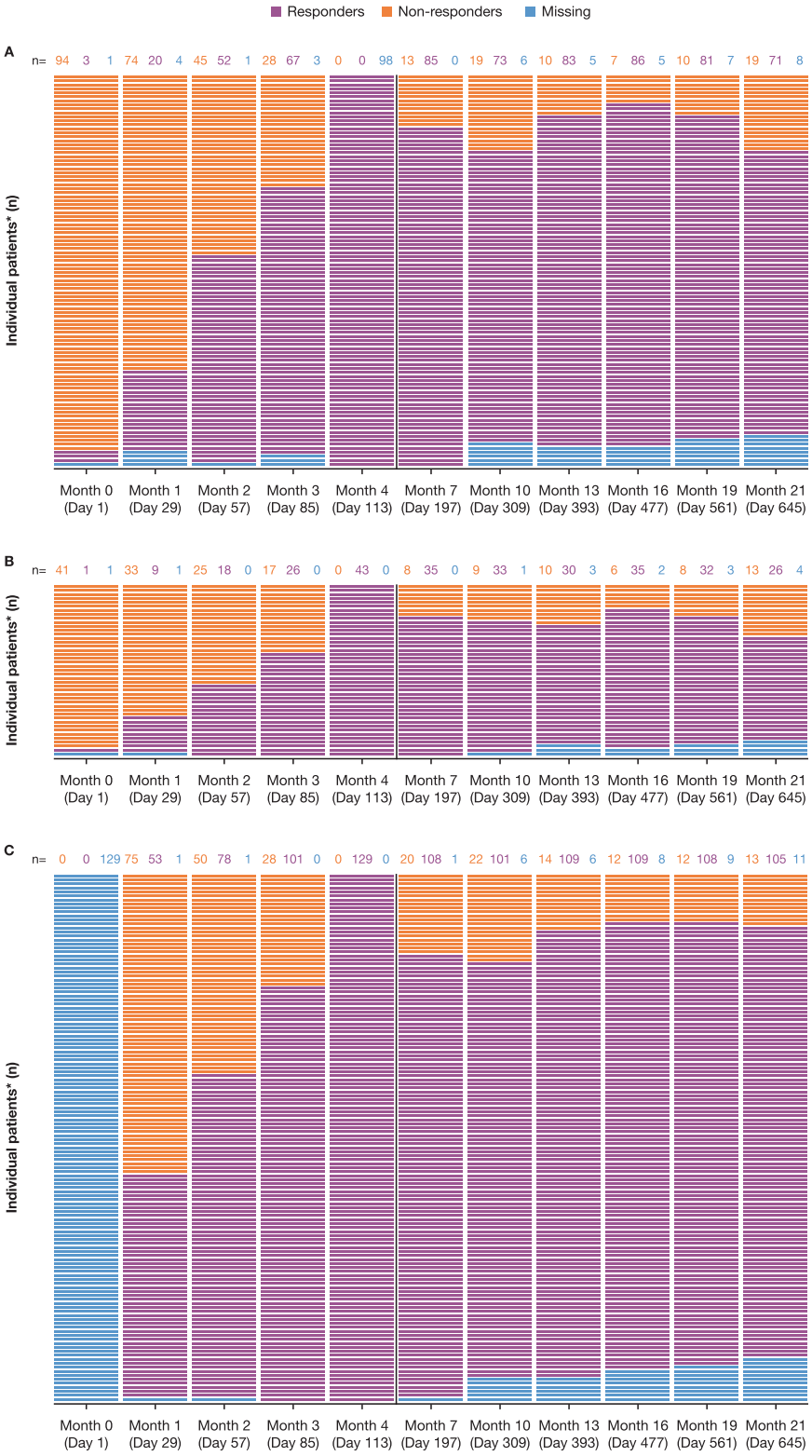

Figure 2. Heat maps of individual patients treated with subcutaneous abatacept who met composite end points at month 4 and their responder status over time: LDA+pain-min (**A**), LDA+CHAQ-DI0 (**B**), and ACR50+pain-min (**C**). Responders are patients who met composite end points. Patients with missing data are imputed as nonresponders. Each bar represents the outcomes achieved over time by a single individual patient. * = each horizontal row represents an individual patient. ACR50+pain-min = 50% improvement in Juvenile Idiopathic Arthritis–American College of Rheumatology criteria plus minimal pain; LDA = low disease activity; LDA+pain-min = LDA plus minimal pain; LDA+CHAQ-DI0 = LDA plus Childhood Health Assessment Questionnaire-disability index score of 0.

the study of SC abatacept are supported by data from the IV abatacept trial, which also showed that the stringent composite end points were achieved by individual patients by month 4, most notably for ACR50+pain-min. Once achieved, composite end points were generally maintained through month 21. In patients receiving SC abatacept, changes over time showed that individual patients who achieved composite end points early maintained them through month 21.

SC abatacept is known to be beneficial in treating children with polyarticular-course JIA with respect to clinical and patient-reported outcomes. Abatacept administered intravenously has been shown to maintain clinical efficacy (ACR30) and patient-reported outcome (mean C-HAQ DI) responses over a 5-year follow-up period (5). However, individual patients can achieve and lose response during a clinical trial, which may not be reflected in group-level data. Therefore, it is important to ascertain if individual children can not only achieve optimal traditional clinical outcomes and patient-reported outcome end points but also sustain them over time. The present research builds on previous population/aggregate analyses in which children with polyarticular-course JIA were successfully treated with SC abatacept (3,5) to show that individual children can achieve and maintain rigorous efficacy end points over time. Similarly, the results from individual patients treated with IV abatacept support the sustainability of composite end points (4).

While the present study reports the possible trajectory of an individual patient who achieves early composite end points, efforts to identify patients who are most likely to achieve an initial treatment response are ongoing. The identification of distinct patient groups as defined by disease manifestation or trajectories of progression, and of prognostic factors for response to abatacept, may help treatment plans for individuals with JIA.

One of the potential limitations of this study may be that we newly defined composite end points. However, the stringent end points we chose are well founded based on current knowledge (3,9–13,15). Additionally, we avoided any thresholds of combined clinical and patient-reported outcome assessments that would be unlikely or impossible to be shared by the same individual (e.g., ACR30 and pain-VAS of 0 mm). The pairing of other clinical and patient-reported outcome end points may either show similar or different results. Furthermore, although this study does not use the latest proposed JADAS-27 cutoffs, the use of previously well-established cutoffs, which were endorsed by professional organizations and used during the interim period of the medical community's transition to the more recent cutoffs, is scientifically valid.

These novel composite end points may be used in future treat-to-target studies, with appropriate input from clinicians and additional validation within a more generalizable JIA population. The data from this post hoc analysis must be interpreted in the context of the initial study populations being a single-arm, open-label SC abatacept trial and a withdrawal trial of patients who achieved an initial response to IV abatacept.

This study demonstrated that individual children with polyarticular-course JIA treated with SC or IV abatacept who achieved stringent composite end points maintain these end points over 21 months. This information may support the development of further treat-to-target strategies and aid discussions among families and care providers for children and adolescents with polyarticular-course JIA.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Brunner had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Brunner, Avila-Zapata, Horneff, Wong, Zhuo, Martini, Lovell, Ruperto.

Acquisition of data. Brunner, Tzaribachev, Louw, Penades, Avila-Zapata, Horneff, Foeldvari, Kingsbury, Gastanaga, Wouters, Breedt, Askelson, Martini, Lovell, Ruperto.

Analysis and interpretation of data. Brunner, Tzaribachev, Louw, Avila-Zapata, Horneff, Foeldvari, Wouters, Wong, Askelson, Zhuo, Martini, Lovell, Ruperto.

ROLE OF THE STUDY SPONSOR

Bristol Myers Squibb had no role in the study design or in the collection, analysis, or interpretation of the data, the writing of the manuscript, or the decision to submit the manuscript for publication. Publication of this article was not contingent upon approval by Bristol Myers Squibb.

ADDITIONAL DISCLOSURES

Authors Zhuo and Askelson are employees of Bristol Myers Squibb.

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