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ORIGINAL RESEARCH

Occurrence of adverse events and change in disease activity after initiation of etanercept in paediatric patients with juvenile psoriatic arthritis in the CARRA Registry

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ABSTRACT

Objective Etanercept is commonly used to treat juvenile idiopathic arthritis, including juvenile psoriatic arthritis (JPsA); however, information on etanercept's safety and effectiveness in clinical practice is limited. We used data from the Childhood Arthritis and Rheumatology Research Alliance (CARRA) Registry to evaluate etanercept's safety and effectiveness in JPsA in clinical practice.

Methods We analysed safety and effectiveness data for paediatric patients enrolled in the CARRA Registry who had a JPsA diagnosis and had used etanercept. Safety was assessed by calculating rates of prespecified adverse events of special interest (AESIs) and serious adverse events (SAEs). Effectiveness was assessed by a variety of disease activity measures.

Results Overall, 226 patients had JPsA and received etanercept; 191 met criteria for safety analysis and 43 met criteria for effectiveness analysis. AESI and SAE incidence rates were low. There were five events: three uveitis, one new-onset neuropathy and one malignancy. Incidence rates were 0.55 (95% CI: 0.18, 1.69), 0.18 (95% CI: 0.03, 1.29) and 0.13 (95% CI: 0.02, 0.09) per 100 patient-years for uveitis, neuropathy and malignancy, respectively. Etanercept showed effectiveness for JPsA treatment; 7 of 15 (46.7%) had an American College of Rheumatology-Pediatric Response 90, 9 of 25 (36.0%) had a clinical Juvenile Arthritis Disease Activity Score 10-joint ≤1.1 and 14 of 27 (51.9%) had clinically inactive disease at the 6-month follow-up.

Conclusion Data in the CARRA Registry showed that etanercept treatment was safe in treating children with JPsA, with low AESIs and SAEs. Etanercept was also effective, even when assessed in a small sample size.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Juvenile psoriatic arthritis (JPsA) is one of seven categories of juvenile idiopathic arthritis (JIA) and constitutes approximately 5% of JIA.

⇒ Etanercept is commonly used to treat JIA, including JPsA; however, information on the safety and effectiveness of etanercept in treatment of patients with JPsA in real-world clinical practice is limited. Here, we evaluated etanercept's safety and effectiveness in JPsA using data from the Childhood Arthritis and Rheumatology Research Alliance (CARRA) Registry, which contains data from over 10 000 children with JIA.

WHAT THIS STUDY ADDS

⇒ Results from analysis of data in the CARRA Registry showed that etanercept treatment in JPsA was effective at 6 months of follow-up and remained effective at 12 months, with low rates of adverse events of special interest (including malignancy and uveitis) and serious adverse events.

⇒ The analysis also showed that etanercept dosing for JPsA was consistent with the product label dose for JIA of 0.8 mg/kg weekly, with a maximum of 50 mg/week.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ These results inform treatment choice for JPsA, supporting the use of etanercept as a safe and effective treatment option in this disease setting, including in children under 12 years old, an age group for whom there is no drug approval.

INTRODUCTION

Juvenile psoriatic arthritis (JPsA) is one of seven categories of juvenile idiopathic arthritis (JIA) and constitutes approximately 5% of JIA.[1 2] According to the International League of Associations for Rheumatology (ILAR), JPsA is classified by chronic arthritis before age 16 years, which is associated with either psoriasis or at least two of the following:

dactylitis, nail pitting, onycholysis or psoriasis in a first-degree relative.[3]

JPsA has a bimodal distribution based on age at onset.[1 4–6] JPsA occurring in children 1–4 years of age is categorised as early onset and typically manifests as peripheral arthritis involving a few joints, whereas JPsA occurring in children over 4 years of age is categorised as older onset and more commonly has features of adult psoriatic arthritis, including spondyloarthritis with increased risk of axial joint involvement and enthesitis.[1 5–7] Dactylitis and uveitis are common clinical features of both early-onset and older-onset JPsA.[1 5 6 8]

Prior to the approval of secukinumab for treatment of JPsA in December 2021,[9] etanercept was the only biologic treatment approved for JPsA (in children over 12 years old) in the European Union[10]; however, etanercept is not yet approved for JPsA in the USA.[11] The low incidence of JPsA[1 2] makes systematic collection of data on treatment outcomes challenging. As such, information on the safety and effectiveness of etanercept in treatment of patients with JPsA in real-world clinical practice is limited. The Childhood Arthritis and Rheumatology Research Alliance (CARRA) Registry is comprised of paediatric rheumatology research centres dedicated to advancing the field of paediatric rheumatology and contains data from over 10 000 children with JIA.[2] In this study, we analysed data from the CARRA Registry to evaluate the safety and effectiveness of etanercept in JPsA.

METHODS

Data source, study design and patient population

The CARRA Registry was started in 2015. The general design and rationale of the registry and the characteristics of patients enrolled have been previously described in detail.[2] Briefly, the CARRA Registry is an international observational registry of paediatric patients with rheumatic diseases, including JIA. At the inception of the registry, there was selective enrolment of paediatric patients who were most likely to be treated with biologics. The registry includes retrospective data collected at the time of enrolment and prospective observational data collected approximately every 6 months at patient visits in the context of routine clinical care and ideally at the time of initiation of any new JIA medication.[2] Data collected include physician-assigned ILAR category, detailed medication logs, clinical features, laboratory data, imaging results and adverse events of special interest (AESIs), including serious adverse events (SAEs). The CARRA Registry also collects the clinical Juvenile Arthritis Disease Activity Score with an active joint count up to 10 (clinical Juvenile Arthritis Disease Activity Score 10-joint (cJADAS-10)), patient-reported outcomes, Childhood Health Assessment Questionnaire, the patient/parent global assessment and pain intensity.[2 12 13]

The present analysis used CARRA Registry data from approximately 70 clinical sites in the USA and Canada beginning 30 June 2015 until the data cut-off date for this analysis of 2 August 2021. Data were analysed for patients aged ≥2–<18 years at etanercept initiation who had a JPsA diagnosis as determined by a rheumatologist and had ever used etanercept. Patients were excluded from the analysis if they had an overlap >31 days of other biologics use after the start of etanercept and follow-up (etanercept start date for incident use or registry enrolment date for ongoing etanercept use) and/or a history of other rheumatic diseases.

The safety cohort included patients who had received etanercept at any time after enrolment in the registry; the effectiveness cohort included patients with a registry visit within 14 days from etanercept initiation (ie, treatment inception cohort). Patients in the effectiveness cohort were etanercept naïve. Baseline period data were collected at the start of follow-up; consequently, different lengths of time constituted the baseline period for patients depending on the time elapsed between disease onset and enrolment (for ongoing etanercept users) or etanercept initiation. Start dates for study follow-up time at risk were based on receipt of etanercept during participation in the CARRA Registry. Follow-up was censored at date of death, registry discontinuation date, latest data collection date or specific censoring dates for each cohort. For the assessment of non-malignancy safety events, study follow-up started at initiation of incident use of etanercept or at registry enrolment for patients with ongoing use of etanercept. Follow-up was censored 91 days after starting another biologic disease-modifying antirheumatic drug (DMARD) or 91 days after discontinuing etanercept unless restarted within those 91 days. For the assessment of malignancy safety events, study follow-up started at initiation of incident use of etanercept or at registry enrolment for patients with ongoing use of etanercept. Follow-up was not censored because of discontinuation of etanercept or initiation of other biologic therapy. For the effectiveness cohort, study follow-up started at initiation of etanercept therapy and continued during ongoing uninterrupted etanercept use until outcomes were assessed. Follow-up was censored 91 days after starting another biologic DMARD or 91 days after discontinuing etanercept unless restarted within those 91 days.

Study outcomes

Baseline characteristics including patient demographics, duration of disease and concomitant use of non-biologic therapy were assessed at the registry visit closest to start of follow-up for etanercept receipt for the safety and effectiveness cohorts. For the effectiveness cohort only, baseline characteristics including disease activity/severity measures were assessed at the registry visit ±14 days from start of etanercept.

Safety was assessed by calculating the rates of 31 prespecified AESIs (see online supplemental table 1 for the complete list) and SAEs in the safety cohort. Effectiveness was assessed by determining changes in the American College of Rheumatology (ACR)-Pediatric

Response (ACR-Pedi Response: 30/50/70/90/100),[14] cJADAS-10[12 15 16] and ACR provisional inactive disease criteria[17] (see online supplemental table 2 for definition of outcomes) assessed at the 6-month and 12-month study follow-up visits in the effectiveness cohort. The 6-month follow-up included patients who were ≤9 months post-etanercept initiation at time of data cut-off or who had completed a registry visit 3–9 months post-etanercept start; if more than one visit was completed in the period 3–9 months post-etanercept initiation window, the visit closest to 183 days post-etanercept initiation was selected. The 12-month follow-up included patients who were ≤15 months post-etanercept initiation at time of data cut-off or who had a completed registry visit 9–15 months post-etanercept start; if more than one visit was completed in the 9–15 months post-etanercept initiation window, the visit closest to 365 days post-etanercept initiation was selected. The starting dose of etanercept expressed as weekly mg/kg was assessed for the effectiveness cohort only, based on recorded patient weight (at the visit closest to etanercept initiation) and administered dose of etanercept.

Statistical analysis

Summary statistics are presented using means, SDs, medians and IQRs (quartile 1 (Q1), quartile 3 (Q3)) for continuous variables and proportions for categorical variables with 95% CIs. AESI and SAE rates are presented as counts per 100 person-years of study follow-up at risk with 95% CIs. ACR-Pedi, cJADAS-10 and ACR provisional clinical inactive disease responses at 6-month and 12-month follow-up visits were assessed in three ways: (1) restricted to patients with ongoing etanercept use and outcome data available at respective 6-month and 12-month intervals from etanercept start (ie, complete case analysis); (2) the outcome from the last visit with ongoing etanercept use was carried forward for patients with missing outcome data or who discontinued etanercept before outcome determination (ie, last observation carried forward (LOCF)), as a sensitivity analysis; and (3) non-response was assumed for patients with missing outcome data or who discontinued etanercept before outcome ascertainment (ie, non-responder imputation (NRI)), as another sensitivity analysis.

RESULTS

Baseline patient demographics and disease activity

Overall, 3155 paediatric patients with JIA in the CARRA Registry had received etanercept and were screened for eligibility for this analysis. Of the 3155 patients, 226 patients had JPsA and of these, 191 met criteria for the safety cohort. The 191 patients in the safety cohort were predominantly white (80.6%) and female (66.0%) (table 1). At the start of follow-up for this analysis, median age in the safety cohort was 12.0 years and median disease duration was 2.4 years. Fifty-six per cent of the patients were taking etanercept at the time they enrolled in the CARRA Registry with a median of 14.9 months (mean of 29.5 months) of etanercept use before registry enrolment. Median age of etanercept initiation was 10.0 years. More than half (59.2%) of the patients had concomitant use of a non-biologic DMARD at the start of follow-up, with most (56.0% of all patients; 94.7% of concomitant non-biologic DMARD users) receiving methotrexate.

Of the 226 patients with JPsA and etanercept exposure, 43 met the criteria for the effectiveness cohort. Patients

Table 1 Baseline characteristics of patients in the safety cohort

Characteristic	Safety cohort N=191
Age at etanercept start, median (Q1, Q3), years	10.0 (6.0, 14.0)
Age at start of follow-up, median (Q1, Q3), years	12.0 (8.0, 15.0)
Sex, n (%)	
Female	126 (66.0)
Male	65 (34.0)
Race, white, n (%)	154 (80.6)
Disease duration at start of follow-up, median (Q1, Q3), years	2.4 (0.5, 5.3)
Concomitant use of non-biologic therapy at start of follow-up, n (%)	113 (59.2)
Methotrexate	107 (56.0)
Leflunomide	4 (2.1)
Sulfasalazine	5 (2.6)
Any etanercept use before CARRA Registry enrolment, n (%)	119 (62.3)
Number of patients with biologic use prior to etanercept, n (%)	17 (8.9)
Adalimumab, n (%)	16 (8.4)
Tocilizumab, n (%)	1 (0.5)
Ongoing etanercept use at time of CARRA Registry enrolment, n (%)	107 (56.0)
Among patients with ongoing etanercept use at time of CARRA Registry enrolment	
Cumulative duration of etanercept use before CARRA Registry enrolment	
Mean (SD), months (number of patients with available data)	29.5 (32.4) (107)
Median (Q1, Q3), months (number of patients with available data)	14.9 (5.8, 38.8) (107)
Elapsed time since etanercept initiation	
Mean (SD), months (number of patients with available data)	31.0 (33.7) (107)
Median (Q1, Q3), months (number of patients with available data)	15.9 (5.8, 42.9) (107)

N=number of patients who met the criteria for the safety cohort, that is, had a rheumatologist-diagnosed JIA category of PsA, did not have ongoing concurrent biologic use at etanercept initiation and had observed time on etanercept during CARRA Registry enrolment; n=number of patients with the characteristic.
CARRA, Childhood Arthritis and Rheumatology Research Alliance; JIA, juvenile idiopathic arthritis; PsA, psoriatic arthritis; Q1, quartile 1; Q3, quartile 3.

in the effectiveness cohort had similar demographics to those in the safety cohort (table 2). The start of follow-up time for the effectiveness cohort was defined as when etanercept was initiated, so this cohort had a shorter disease duration at start of follow-up (median 0.4 years) compared with the safety cohort (median 2.4 years). Median physician global assessment of disease activity was 3.5, median patient/parent global assessment of overall well-being was 3.0, 27.9% of patients had active psoriasis skin lesions reported and median cJADAS-10 was 10.0. No patients had active uveitis at etanercept initiation.

Rates of AESIs and SAEs with etanercept in the safety cohort

The 191 patients in the safety cohort had a low incidence of AESIs, SAEs and malignancy (table 3). The incidence of AESIs (excluding malignancy) was based on the three cases of uveitis (non-serious) reported during the observed use of etanercept, with an incidence rate of new-onset uveitis of 0.55 (95% CI: 0.18, 1.69) per 100 person-years. All three new-onset uveitis events were consistent with JIA-associated uveitis and responded clinically to treatment with topical glucocorticoid eye drops. The three patients with uveitis (patients 1, 2 and 3) had been diagnosed with JIA at ages 2.4, 3.4 and 9.4 years, respectively, and were diagnosed with uveitis at ages 4.3, 5.7 and 10.0 years, respectively. Patient 1 had been taking etanercept only at the time of uveitis onset; patients 2 and 3 had been treated with etanercept and methotrexate.

One SAE of new-onset neuropathy was reported, for an overall rate of 0.18 (95% CI: 0.03, 1.29) per 100 person-years during observed use of etanercept. The new-onset neuropathy occurred approximately 4 months after initiation of etanercept. The patient was concurrently treated with methotrexate. The patient who experienced the event had tingling sensation of the foot that was classified as medically significant by the investigator, indicating the potential to escalate to another serious outcome if not treated. The event ultimately resolved and was not considered suggestive of demyelination. Etanercept use was continued following the event.

In the specific assessment for malignancy following etanercept use, one AESI of malignancy was reported representing an overall rate of 0.13 (95% CI: 0.02, 0.90) per 100 person-years during 789.2 person-years of follow-up including observed time after discontinuation of etanercept. The patient who experienced the malignancy presented with an abdominal mass that was diagnosed as a liver sarcoma by biopsy specimen approximately 30 months after initiation of etanercept. The patient had a history of prior treatment with adalimumab and methotrexate and was taking etanercept and methotrexate at the time of the malignancy diagnosis.

ACR-Pedi, cJADAS-10 and ACR provisional clinical inactive disease responses with etanercept in the effectiveness cohort

Of the 43 patients in the effectiveness cohort, 32 had evaluable data for the reported outcomes and

Table 2 Baseline characteristics of patients in the effectiveness cohort

Characteristic	Effectiveness cohort N=43
Age at etanercept start, median (Q1, Q3), years	10.0 (7.0, 13.0)
Sex, n (%)	
Female	29 (67.4)
Male	14 (32.6)
White, n (%)	37 (86.0)
Disease duration at start of follow-up, median (Q1, Q3), years	0.4 (0.1, 2.7)
Concomitant use of non-biologic therapy at start of follow-up, n (%)	24 (55.8)
Methotrexate	22 (51.2)
Leflunomide	2 (4.7)
Sulfasalazine	1 (2.3)
Concomitant use of oral glucocorticoid, n (%)	3 (7.0)
Total number of joints with active arthritis*	
Available patients, n (%)	42 (97.7)
Median (Q1, Q3)	4.0 (2.0, 8.0)
Physician global assessment of disease activity*	
Available patients, n (%)	39 (90.7)
Median (Q1, Q3)	3.5 (2.5, 5.0)
Patient/parent global assessment of overall well-being*	
Available patients, n (%)	30 (69.8)
Median (Q1, Q3)	3.0 (1.0, 6.0)
ESR*, mm/hour	
Available patients, n (%)	25 (58.1)
Median (Q1, Q3)	8.0 (5.0, 25.0)
CRP*, mg/L	
Available patients, n (%)	15 (34.9)
Median (Q1, Q3)	0.5 (0.2, 0.7)
Active psoriasis skin lesions reported, n (%)	12 (27.9)
Previous or current dactylitis at the CARRA Registry baseline visit	18 (41.9)
Active uveitis*, n (%)	0 (0)
Past uveitis, n (%)	0 (0)
Morning stiffness*, n (%)	
None	12 (27.9)
≤ 15 min	4 (9.3)
16–60 min	11 (25.6)
> 60 min	9 (20.9)
Unknown	7 (16.3)
cJADAS-10*	

Continued

Table 2 Continued

Characteristic	Effectiveness cohort N=43
Available patients, n (%)	29 (67.4)
Median (Q1, Q3)	10.0 (6.0, 10.0)
Active enthesitis at the study baseline visit	9 (20.9)
Previous or current sacroiliitis at the study baseline visit	10 (23.3)

N=number of patients who met the criteria for the effectiveness cohort, that is, had a registry visit ±14 days from etanercept initiation, had uninterrupted etanercept use and had a 6-month or 12-month follow-up visit; n=number of patients with the characteristic.
*Disease activity data reflective of the visit that occurred within 14 days of etanercept initiation.
CARRA, Childhood Arthritis and Rheumatology Research Alliance; cJADAS-10, clinical Juvenile Arthritis Disease Activity Score 10-joint; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; Q1, quartile 1; Q3, quartile 3.

uninterrupted etanercept use at the 6-month follow-up (table 4). For the 15 patients evaluable for the ACR-Pedi Response at the 6-month follow-up, 80.0% (12 of 15) of the patients showed an ACR30 response and 46.7% (7 of 15) of the patients showed an ACR90 response (figure 1A and table 4). Only five patients were evaluable for the ACR-Pedi Response at the 12-month follow-up, with 80.0% (4 of 5) of the patients showing an ACR30 response and 20.0% (1 of 5) of the patients showing an ACR90 response. For the 25 patients evaluable for cJADAS-10 at the 6-month follow-up, 36.0% (9 of 25) of the patients had cJADAS-10 ≤1.0 (figure 1B and table 4). Only 13 patients were evaluable for the cJADAS-10 at the 12-month follow-up and 53.8% (7 of 13) of these patients had cJADAS-10 ≤ 1.1. Median (Q1, Q3) change from baseline in cJADAS-10 was −2.8 (−6.0, −1.0) at the 6-month follow-up and −5.5 (−7.0, −2.8) at the 12-month follow-up (table 4). The ACR provisional criteria for inactive disease were met by 51.9% (14 of 27) of patients at the 6-month follow-up and 43.8% (7 of 16) of patients at the 12-month follow-up (figure 1C and table 4). Additionally, 55.8% (24 of 43) of patients were concurrently treated with methotrexate at the 6-month follow-up and 39.5% (17 of 43) were taking methotrexate at the 12-month follow-up.

In sensitivity analyses, etanercept effectiveness was determined using LOCF and NRI. By LOCF, the observed effectiveness of etanercept was attenuated; nevertheless, approximately 30% of patients met the ACR provisional criteria for clinical inactive disease at the 6-month follow-up (13 of 41 patients) and 12-month follow-up (10 of 34 patients) (figure 2 and online supplemental table 3). By NRI, which is the most conservative statistical approach, etanercept effectiveness was further attenuated, with the proportions of patients meeting the ACR provisional criteria for clinical inactive disease at the 6-month and 12-month follow-up of 34.1% (14 of 41 patients) and 20.6% (7 of 34 patients), respectively (figure 3 and online supplemental table 4).

Table 3 Rates of AESIs and SAEs among patients with JPsA during observed etanercept use, overall and stratified by sex (incidence rates/100 PYs)

	Female (N=126; PYs=341.2)			Male (N=65; PYs=209.2)			Total (N=191; PYs=550.4)		
Adverse event type	n	Rate	95% CI	n	Rate	95% CI	n	Rate	95% CI
AESIs*									
Uveitis	1	0.29	0.04, 2.08	2	0.96	0.24, 3.82	3	0.55	0.18, 1.69
Infections treated with intravenous anti-infectives	0	0	0	0	0	0	0	0	0
SAEs†	1	0.29	0.04, 2.08	0	0	0, NC	1	0.18	0.03, 1.29
New-onset neuropathy	1	0.29	0.04, 2.08	0	0	0, NC	1	0.18	0.03, 1.29
Malignancy‡									
Any malignancy	1	0.20	0.03, 1.43	0	0	0, NC	1	0.13	0.02, 0.90

N=number of patients who met the criteria for the safety cohort, that is, had a rheumatologist-diagnosed JIA category of PsA, did not have ongoing concurrent biologic use at etanercept initiation and had observed time on etanercept during CARRA Registry enrolment; n=number of AESIs or SAEs.
*Thirty-one AEs were prespecified as AESIs (see online supplemental table 1), including any malignancy and uveitis but malignancy was reported separately.
†Any AE meeting serious criteria; malignancy and uveitis were included in the case report form and therefore 'solicitated' as part of the AESIs, but malignancy was reported separately.
‡Malignancy was reported separately as the follow-up period for time at risk was different from that for AESIs and SAEs; PY=494.8 for females, 294.4 for males and PY=789.2 for total.
AE, adverse event; AESIs, adverse events of special interest; CARRA, Childhood Arthritis and Rheumatology Research Alliance; JIA, juvenile idiopathic arthritis; JPsA, juvenile psoriatic arthritis; NC, not calculable; PsA, psoriatic arthritis; PY, person-year; SAEs, serious adverse events.

Table 4 ACR-Pedi, cJADAS-10 and ACR provisional clinical inactive disease responses with etanercept in the effectiveness cohort by complete case analysis

Outcome	Response	
	At 6-month follow-up N=32	At 12-month follow-up N=22
ACR-Pedi Response, n (%) (number of patients with complete data)		
ACR30	12 (80.0) (15)	4 (80.0) (5)
ACR50	10 (66.7) (15)	4 (80.0) (5)
ACR70	10 (66.7) (15)	3 (60.0) (5)
ACR90	7 (46.7) (15)	1 (20.0) (5)
cJADAS-10		
Median (Q1, Q3) (number of patients with complete data)	2.5 (0.5, 6.0) (25)[21]	0 (0, 3.0) (13)
≤ 1.1, n (%) (number of patients with complete data)*	9 (36.0) (25)	7 (53.8) (13)
≤ 2.5, n (%) (number of patients with complete data)*	13 (52) (25)	9 (69.2)[12] (13)
Change in cJADAS-10, median (Q1, Q3) (number of patients with complete data)	–2.8 (–6.0, –1.0) (18)	–5.5 (–7.0, –2.8) (8)
Active enthesitis present, n (%) (number of patients with complete data)	5 (20.9) (39)	3 (10.0) (30)
ACR provisional clinical inactive disease, n (%) (number of patients with complete data)	14 (51.9) (27)	7 (43.8) (16)

N=number of patients who initiated etanercept after CARRA Registry enrolment, had a registry visit ±14 days from etanercept initiation, had uninterrupted etanercept use and had a 6-month or 12-month follow-up visit; n=number of patients with outcome. Responses could not be calculated for patients with missing observations at the baseline or a follow-up visit.
*Since the cJADAS-10 has not been validated for JPsA, we included cut-off values for inactive disease for oligoarthritis and polyarthritis.
ACR, American College of Rheumatology; ACR-Pedi Response, American College of Rheumatology-Pediatric Response; CARRA, Childhood Arthritis and Rheumatology Research Alliance; cJADAS-10, clinical Juvenile Arthritis Disease Activity Score 10-joint; JPsA, juvenile psoriatic arthritis; Q1, quartile 1; Q3, quartile 3.

Etanercept dosing in the effectiveness cohort

Initial etanercept dosing was determined in the effectiveness cohort (table 5). Thirty-seven patients weighed less than 62.5 kg and the median dose was the etanercept-labelled dose for JIA of 0.8 mg/kg.[11] At least 65% of patients received doses between 0.7 and 0.9 mg/kg. Among six patients weighing greater than 62.5 kg, five (83.3%) received the labelled dose of 50 mg weekly and one (16.7%) received less than 50 mg weekly. No patients received more than the labelled dose of 50 mg weekly.[11]

DISCUSSION

Results from our analysis of data from patients with JPsA enrolled in the CARRA Registry showed that patients receiving etanercept had a low incidence of prespecified AESIs (three incidences of new-onset uveitis and one incidence of malignancy) and SAEs (one incidence of new-onset neuropathy). Etanercept was effective in JPsA treatment as assessed by the ACR-Pedi, cJADAS-10 and ACR provisional clinical inactive disease responses, and maintained effectiveness over 12 months. Additionally, etanercept dosing was consistent with the product label dose for JIA of 0.8 mg/kg weekly, with a maximum of 50 mg/week.[11]

When we consider the safety of biologic therapies, including etanercept, we can categorise safety events in three categories including serious infection, neoplasia and secondary autoimmunity, of which the first two are of highest concern in paediatrics.[18 19] It is important to note that this study did not identify any events of serious infection. One patient developed malignancy. The observed overall incidence rate for the one AESI of malignancy of 0.18 (95% CI: 0.03, 1.29) per 100 person-years is within the range of previously published studies. In the German Biologics in Pediatrics Rheumatology Registry (BiKeR) Study,[20] a malignancy rate of 0.05 (95% CI: 0.02, 0.2) per 100 person-years was reported in paediatric patients with JIA treated with etanercept (three cases of malignancy) and a rate of 0.05 (95% CI: 0.01, 0.2) was reported in paediatric patients with JIA who were biologic-naïve (two cases of malignancy). In a large claims database study in the USA,[21] a malignancy rate of 0.05 per 100 person-years was reported for patients with JIA treated with tumour necrosis factor inhibitors, and a rate of 0.03 per 100 person-years was reported in paediatric patients with JIA who were not treated with tumour necrosis factor inhibitors. Because this is a small study, it is challenging to make conclusions about malignancy risk with only one malignancy event. This highlights the importance of long-term safety monitoring in large databases such as the CARRA Registry. Other than uveitis, which is a known complication of JIA, no patients developed a secondary autoimmune disease. The observed overall incidence rate for the three AESIs of new-onset uveitis of 0.55 (95% CI: 0.18, 1.69) per 100 person-years was substantially lower than that observed in other JIA

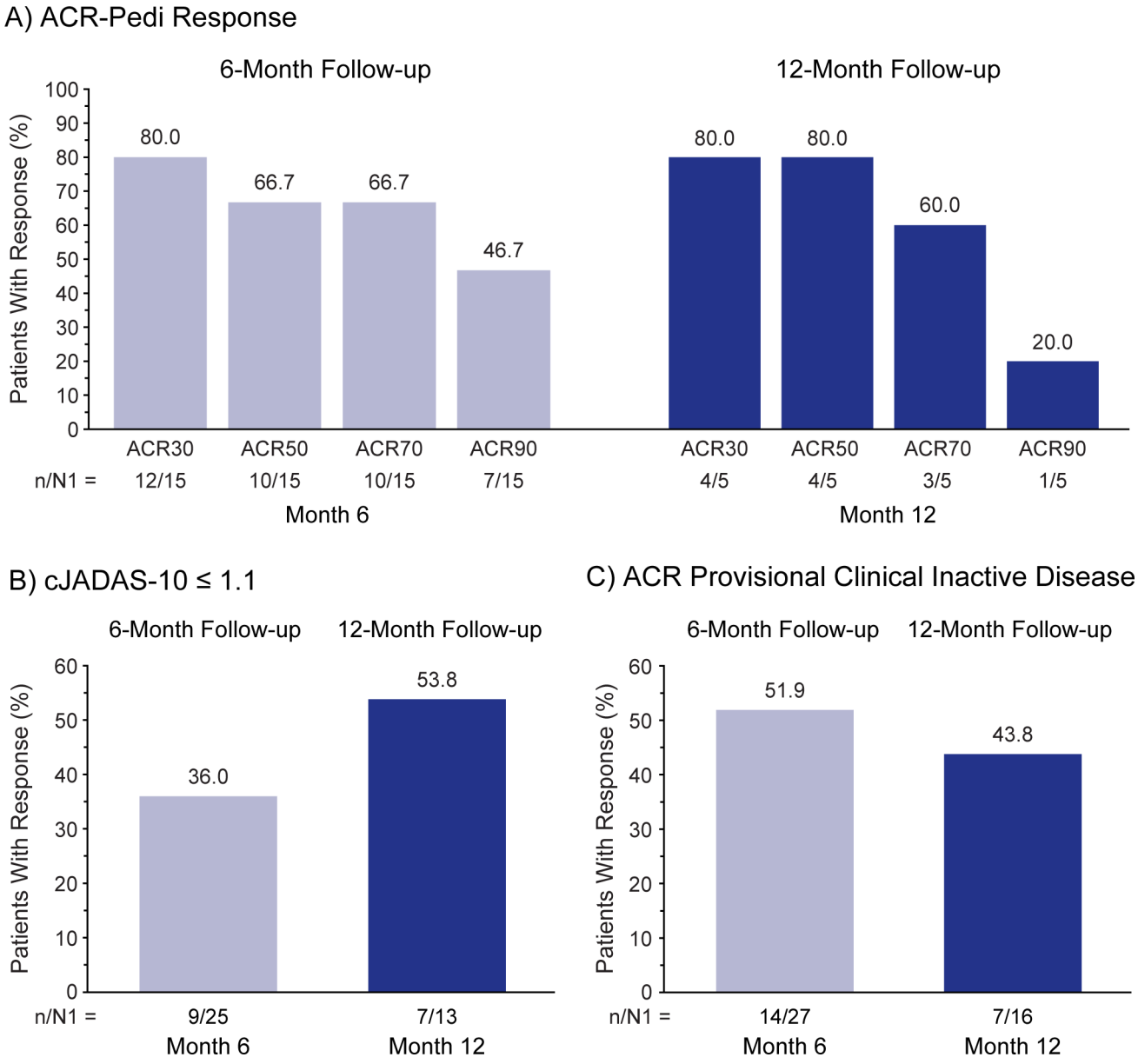

Figure 1 Effectiveness outcomes in patients with JPsA initiating etanercept after CARRA Registry enrolment by complete case analysis: (A) ACR-Pedi Response; (B) cJADAS-10 ≤ 1.1 and (C) ACR provisional clinical inactive disease. The analysis included patients who initiated etanercept after CARRA Registry enrolment, had a registry visit ±14 days from etanercept initiation, had uninterrupted etanercept use and had a 6-month or 12-month follow-up visit. N1=number of patients with complete outcome data available for analysis; n=number of patients with outcome. Responses could not be calculated for patients with missing observations at the baseline or a follow-up visit. ACR, American College of Rheumatology; ACR-Pedi Response, American College of Rheumatology-Pediatric Response; CARRA, Childhood Arthritis and Rheumatology Research Alliance; cJADAS-10, clinical Juvenile Arthritis Disease Activity Score 10-joint; JPsA, juvenile psoriatic arthritis.

cohorts,[20 22–24] most likely because our analysis focused on a subpopulation with JPsA and did not include the population with oligoarthritis JIA that has a higher risk of uveitis. One patient developed neuropathy, but this was not thought to be a demyelinating disease. The observed SAE rate for the one incidence of new-onset neuropathy of 0.18 (95% CI: 0.03, 1.29) per 100 person-years in our analysis is substantially lower than SAE rates of 3.8 (95% CI: 3.3, 4.3) per 100 person-years reported in patients with JIA treated with etanercept and 1.4 (95% CI: 1.1, 1.8) per 100 person-years in patients with JIA who were biologic-naïve as reported in the BiKeR Study.[20] This is also lower than the SAE rate of 3.3 per 100 person-years reported in a long-term (6-year) follow-up of the open-label clinical trial of etanercept for the treatment of JPsA.[25] Of note, in our analysis, 62% of patients in the safety cohort had initiated etanercept, a mean of more than 2 years before enrolment in the study, and ongoing or recurrent users of etanercept would be expected to have fewer SAEs than new initiators. However, the nature of SAE reporting in the CARRA Registry may also contribute to the lower than anticipated observed event

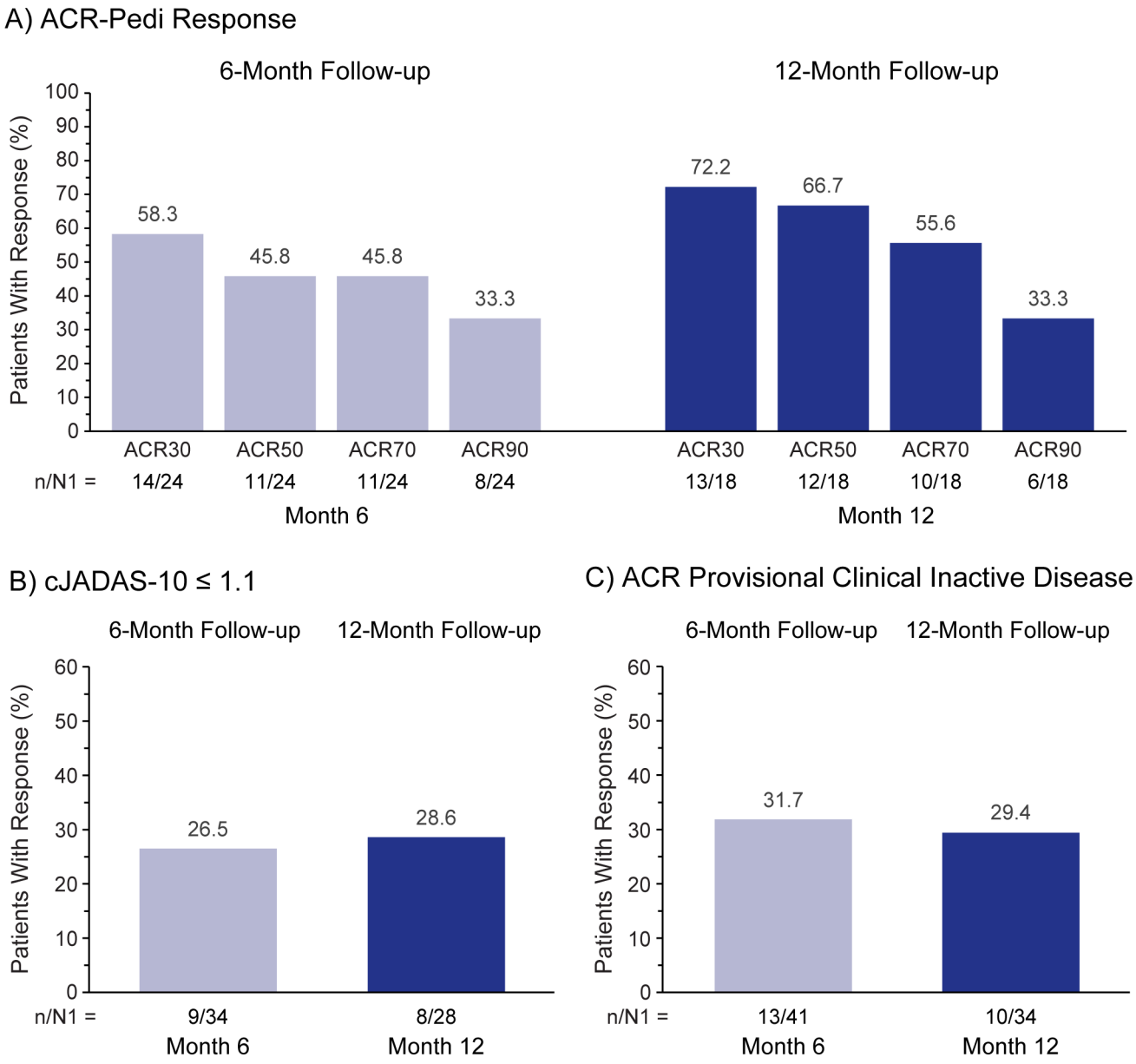

Figure 2 Effectiveness outcomes in patients with JPsA initiating etanercept after CARRA Registry enrolment by LOCF (sensitivity analysis): (A) ACR-Pedi Response; (B) cJADAS-10 ≤ 1.1 and (C) ACR provisional clinical inactive disease. The analysis included patients who initiated etanercept after registry enrolment, had a registry visit ±14 days from etanercept initiation and had at least 6 or 12 months of follow-up time (irrespective of continued etanercept use or follow-up visit data collection). N1=number of patients with complete outcome data available for analysis, including LOCF; n=number of patients with outcome. Responses could not be calculated for patients with missing observations at the baseline or a follow-up visit. ACR, American College of Rheumatology; ACR-Pedi Response, American College of Rheumatology-Pediatric Response; CARRA, Childhood Arthritis and Rheumatology Research Alliance; cJADAS-10, clinical Juvenile Arthritis Disease Activity Score 10-joint; JPsA, juvenile psoriatic arthritis; LOCF, last observation carried forward.

rate (ie, the clinical sites may not be aware of the occurrence of all SAEs).

Etanercept administered at the labelled dose for JIA of 0.8 mg/kg weekly, with a maximum of 50 mg/week,[11] appeared to be effective for the treatment of JPsA, although the interpretation of results was limited by missing clinical measures. Of the 43 patients in the effectiveness cohort, 15 patients were evaluable for the ACR-Pedi Response at the 6-month follow-up and 5 at the 12-month follow-up. Overall, etanercept treatment showed effectiveness by ACR30/50/70/90/100 response criteria, cJADAS-10, and ACR provisional clinical inactive disease criteria. However, in the most conservative statistical approach with missing data treated as treatment failure (NRI), the observed effectiveness of etanercept was substantially attenuated.

Etanercept effectiveness observed in our analysis is consistent with that reported in earlier studies. In our analysis, the proportions of patients with ACR30/50/70 were 80.0%, 66.7% and 66.7%, respectively, among

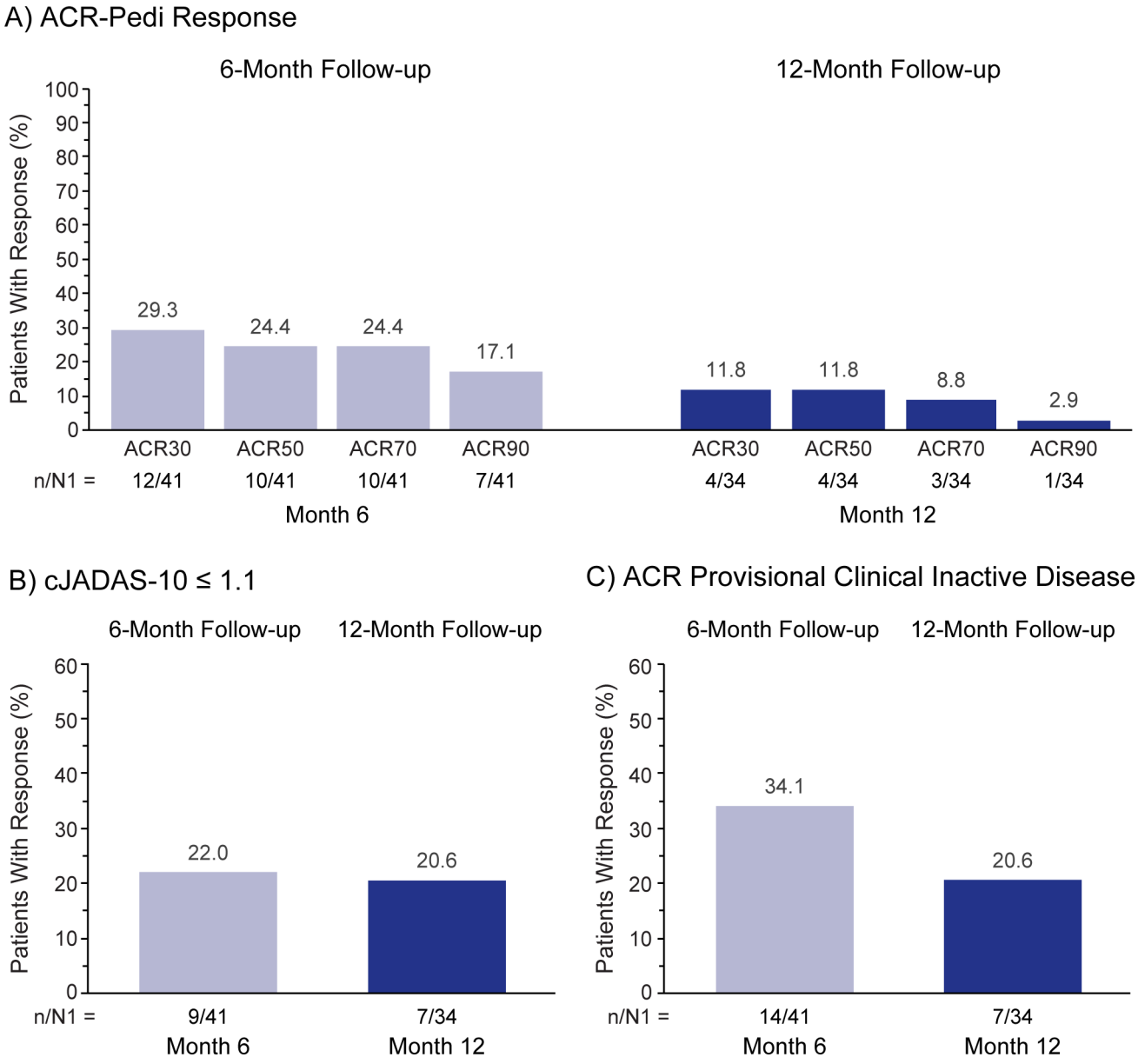

Figure 3 Effectiveness outcomes in patients with JPsA initiating etanercept after CARRA Registry enrolment by NRI (sensitivity analysis): (A) ACR-Pedi Response; (B) cJADAS-10 ≤ 1.1 and (C) ACR provisional clinical inactive disease. The analysis included patients who initiated etanercept after registry enrolment, had a registry visit ±14 days from etanercept initiation and had at least 6 or 12 months of follow-up time (irrespective of continued etanercept use or follow-up visit data collection). N1=number of patients with calculable outcomes, with missing data treated as non-response; n=number of patients with outcome. Responses could not be calculated for patients with missing observations at the baseline or a follow-up visit. ACR, American College of Rheumatology; ACR-Pedi Response, American College of Rheumatology-Pediatric Response; CARRA, Childhood Arthritis and Rheumatology Research Alliance; cJADAS-10, clinical Juvenile Arthritis Disease Activity Score 10-joint; JPsA, juvenile psoriatic arthritis; NRI, non-responder imputation.

the 15 patients with complete data and uninterrupted etanercept use at the 6-month follow-up. Similar overall results were reported in the open-label clinical trial of etanercept for the treatment of JPsA that included 29 patients,[26 27] and showed approximate proportions of patients with ACR30/50/70 of 90%, 90% and 60%, respectively. The BiKeR Study in JIA also showed similar results, with reported ACR30/50/70 response rates of 82%, 79% and 71%, respectively, after 9 years of treatment with etanercept.[20]

Our analysis has a number of limitations. First, the baseline assessment was up to 14 days after initiation of etanercept, which for some patients may have underestimated disease activity at etanercept onset. Additionally, the assessment of effectiveness was limited by the availability of clinical data in this observational registry study. For much of the effectiveness data, our sample sizes were quite small, as small as five patients in some cases, and thus we cannot be certain that our effectiveness findings are representative of the population with JPsA as a whole.

Table 5 Etanercept dosing in the effectiveness cohort

Dosing characteristic	Effectiveness cohort N=43
Restricted to patients weighing < 62.5 kg at etanercept initiation	
Weekly etanercept dose at initiation, median (Q1, Q3), mg/kg (number of patients with available data)	0.8 (0.8, 0.9) (37)
Restricted to patients weighing ≥ 62.5 kg at etanercept initiation, n (%) (number of patients with available data)	
Received 50 mg weekly	5 (83.3) (6)
Received > 50 mg weekly	0 (0) (6)
Received <50 mg weekly	1 (16.7) (6)

N=number of patients who met the criteria for the effectiveness cohort, that is, initiated etanercept after CARRA Registry enrolment, had a registry visit ±14 days from etanercept initiation had uninterrupted etanercept use, and had a 6-month or 12-month follow-up visit. Dosing calculation reflects the weight at visit closest to the time of etanercept initiation (within 9 months before 9 months post-initiation); no patients were excluded due to no weight available for dose calculation.
CARRA, Childhood Arthritis and Rheumatology Research Alliance; Q1, quartile 1; Q3, quartile 3.

To assess the ACR-Pedi Response criteria, clinical data at the time of treatment initiation are required. Among 72 patients who initiated etanercept after CARRA Registry enrolment, 26 (36.1%) did not have all of the required baseline clinical data for inclusion in the effectiveness assessment. Among patients included in the effectiveness assessment, there were patients with missing follow-up visits or patients with missing clinical assessments for the visits that occurred. Traditional clinical trial single imputation methods (ie, LOCF) were limited because the 6-month follow-up was typically the first data collection point following etanercept initiation. Inflammatory markers were not always assessed during clinic visits, which limited the utility of the ACR-Pedi Response criteria. Due to missing data for the parent global assessment of overall well-being, the ACR provisional criteria for clinical inactive disease was calculable for a greater proportion of patients compared with the ACR-Pedi Response criteria and cJADAS-10. It is possible that not all safety events were reported to the CARRA Registry. We did not assess rate or reason for discontinuation of etanercept in patients with JPsA because it was beyond the scope of this study, but it is likely that the rates and reasons for discontinuation are similar to those seen in a previous study of all etanercept use in the CARRA Registry.[28] Sites report safety events as they become aware of their occurrence, which may result in incomplete or delayed identification of events, especially those that occur remotely from the rheumatology care centre's institution. Given that the CARRA Registry remains active and open for data collection, there is also the potential that additional safety events will be identified and reported after publication of this study. Further, our analysis did not evaluate whether there is a difference in etanercept effectiveness in axial and non-axial peripheral JPsA. Finally, no comparator groups of patients who received treatments other than etanercept were included in our analysis.

Results from our analysis of data in the CARRA Registry showed that etanercept treatment in JPsA was effective over 12 months, with low rates of AESIs and SAEs; however, further research is needed to evaluate whether there is a difference in etanercept effectiveness in axial and non-axial peripheral JPsA, and whether the effectiveness is sustained in the longer term. No signals were observed to suggest that etanercept is less effective or safe in JPsA than JIA in general.

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