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Original article

Long-term surveillance of biologic therapies in systemic-onset juvenile idiopathic arthritis: data from the German BIKER registry

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Abstract

Objective. Using data from the German Biologics JIA Registry (BIKER), long-term safety of biologics for systemic-onset JIA with regard to adverse events of special interest was assessed.

Methods. Safety assessments were based on adverse event reports after first dose through 90 days after last dose. Rates of adverse event, serious adverse event and 25 predefined adverse events of special interest were analysed. Incidence rates were compared for each biologic against all other biologics combined applying a mixed-effect Poisson model.

Results. Of 260 systemic-onset JIA patients in this analysis, 151 patients received etanercept, 109 tocilizumab, 71 anakinra and 51 canakinumab. Patients with etanercept had higher clinical Juvenile Arthritis Disease Activity Score 10 scores, active joint counts and steroid use at therapy start. Serious adverse events were reported with higher frequency in patients receiving canakinumab [20/100 patient years (PY)] and tocilizumab (21/100 PY). Cytopenia and hepatic events occurred with a higher frequency with tocilizumab and canakinumab. Medically important infections were seen more often in patients with IL-6 or IL-1 inhibition. Macrophage activation syndrome occurred in all cohorts with a higher frequency in patients with canakinumab (3.2/100 PY) and tocilizumab (2.5/100 PY) *vs* anakinra (0.83/100 PY) and etanercept (0.5/100 PY). After adjustment only an elevated risk for infections in anakinra-treated patients remained significant. Three definite malignancies were reported in patients ever exposed to biologics. Two deaths occurred in patients treated with etanercept.

Conclusion. Surveillance of pharmacotherapy as provided by BIKER is an import approach especially for patients on long-term treatment. Overall, tolerance was acceptable. Differences between several biologics were noted and should be considered in daily patient care.

Key words: juvenile idiopathic arthritis, systemic-onset, Still's disease, treatment, biologics, etanercept, tocilizumab, anakinra, canakinumab, safety, adverse event

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Rheumatology key messages

- Monitoring of biologic therapies in long-term treatment of systemic-onset JIA remains an important task.
- Medically important infections and cytopenias were the most common reported events in systemic-onset JIA patients
- Macrophage activation syndrome occurs upon biologic treatment in patients with systemic-onset JIA.

Introduction

Systemic-onset juvenile idiopathic arthritis (soJIA) is a severe subtype of JIA accounting for about 10% of JIA cases [1] with risk of higher mortality. It is characterized by arthritis accompanied or preceded by systemic inflammation characteristically presenting as spiking fever and rash with elevated laboratory parameters of inflammation. Hepatosplenomegaly, lymphadenopathy and serositis may be present [2]. However, the underlying inflammatory process appears to be distinct from other JIA categories with a prominent autoinflammatory component including a central role for IL-1 and IL-6 [3, 4]. Treatments specifically targeting IL-1 and IL-6 are now available, and efficacy has been demonstrated in randomized controlled trials [5–9]. Up to one-third of soJIA patients show a monophasic course with resolution of all symptoms and no recurrences. In the remaining patients, recurring or ongoing systemic inflammation occurs. Some patients develop chronic destructive arthritis without active systemic features. An association with macrophage activation syndrome (MAS) is also a feature of soJIA. MAS is a severe, potentially life-threatening complication characterized by excessive activation of differentiated macrophages, resulting in fever, hepatosplenomegaly, lymphadenopathy, cytopenia, liver disease, intravascular coagulation and neurological involvement [10]. Treatment of these patients remains a challenge. At the beginning of the 'biologic era', many soJIA patients, especially with active arthritis were treated with etanercept (ETA), but TNFα inhibitors (TNFi) did not yield the good response seen in other JIA categories [11–13]. The development of IL-6 and IL-1 inhibiting therapies improved treatment of soJIA on a larger scale. The IL-1 receptor antagonist anakinra (ANA), the monoclonal IL-1β antibody canakinumab (CAN) and the monoclonal antibody against IL-6 tocilizumab (TOC) are approved for treatment of soJIA. Interestingly, early treatment with IL-1 inhibition seems to be associated with a high response rate [14, 15], has been recommended by the ACR [16] and is part of the Childhood Arthritis and Rheumatology Research Alliance consensus treatment plans for soJIA [17].

Long-term data, regarding safety, especially with respect to rarer events, are scarce. In this analysis, data from the German Biologics JIA Registry (BIKER) are evaluated and compared with respect to long-term safety in soJIA patients treated with ETA, TOC, ANA and CAN.

Methods

The German BIKER registry has been prospectively documenting JIA patients treated with biologics since 2001, after ethics committee approval. It is registered in the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP; http://www.encepp.eu/encepp/viewResource.htm?id=20591). BIKER has been described previously [11, 18]. Written informed consent was obtained and pseudonymized data were collected for each patient starting a biologic. Patient assessment was performed at baseline, after 3 and 6 months and every 6 months thereafter. After discontinuation of treatment, patients were prospectively followed up every 6 months. Adult patients are transitioned to the JUMBO registry [19]. Adverse events (AE) are documented at each visit covering the whole period from the last visit. In cases of AE of special interest (AESIs), detailed information about the event is requested from the investigator.

For this analysis patients with the diagnosis of soJIA were selected. ILAR criteria [20] were applied for diagnosis. The majority of documented patients with soJIA in BIKER had been treated with one or more cycles of the following biologics: ETA, TOC, ANA and/or CAN.

Definitions

AE were reported by the paediatric rheumatologist. The AE report includes incident events or reoccurrence of events such as infections. Repeated reports for the same initial event were not considered in the analyses. An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product, and does not necessarily have a causal relationship with this treatment. A serious AE (SAE) is an untoward medical occurrence that at any dose results in death; is life-threatening; requires hospitalization/prolongation of hospitalization; requires medical or surgical intervention to prevent a serious outcome; results in persistent or significant disability/incapacity; or is a congenital anomaly/birth defect [21]. All AE reports are coded according to the Medical Dictionary for Regulatory Activities (MedDRA). For the pharmacosurveillance of the biologics for treatment of soJIA, 25 AESIs were predefined: anaphylaxis, autoimmune disease (including vasculitis), bleeding disorder, inflammatory bowel disease, cytopenia, demyelination, gastrointestinal perforation, hepatic event, medically important infection, malignancy, MAS, cardiovascular event, depression, pregnancy, thrombotic event, uveitis, cerebral insult, systemic lupus erythematosus, opportunistic

infection, inefficacy, hepatitis B-reactivation, arterial hypertension, sarcoidosis, serum sickness and death.

An AE was attributed to the respective biologic if the patient had received this biologic at the time of the occurrence of the AE or within 90 days after discontinuation, with the exception of malignancies. A malignancy was attributed to the biologic if the patient was ever treated with the biologic prior to the onset of malignancy. The drug exposure was censored at the last available visit in the registry. In addition, the combination therapy of biologics with systemic steroids with respect to the risk of AE, SAE and infections was analysed. The exposure to systemic steroids started at the date of the first dose and ended at the date of discontinuation.

Statistical analysis

AE rates were calculated per 100 patient years with 95% exact Poisson confidence intervals. A mixed effect Poisson model was applied to compare the incidence of AE, SAE and AESI between the four groups to account for multiple treatment episodes for a patient. The relative risk for an AE for each biologic was estimated in comparison with the other three biologics combined. The models were adjusted for concomitant use of MTX and steroids at baseline, presence of systemic signs, disease duration, clinical juvenile arthritis disease activity score 10 (cJADAS-10), childhood health assessment questionnnaire (C-HAQ), pain and number of prior treatment cycles with a biologic at start of treatment with ETA, TOC, ANA and CAN. Statistical analyses were conducted with SAS 9.3 (SAS Institute Inc., Cary, NC, USA).

Results

From a total of 4500 JIA patients enrolled in the German BIKER registry, 293 patients had a diagnosis of soJIA. Excluding 32 patients with MTX monotherapy and one patient with adalimumab, 260 patients were eligible for this analysis. The mean follow-up was 4.3 years [S.D. 3.8, median 3.3, 1121 patient years (PY)]. The total exposure time to biologics was 856 exposure years (EY), 151 patients received ETA (397 EY), 109 TOC (244 EY), 71 ANA (121 EY) and 51 CAN (94 EY).

Of the 260 patients, 137 (53%) patients had only one treatment course and 123 (47%) had more than one treatment course with a biologic including the restart of the same biologic or the switch to another biologic. Among the 123 patients, 96 were exposed to more than one biologic during follow-up. The other 27 patients were treated with the same biologic at least in two treatment courses. Over time, the preferred choice of biologic for soJIA treatment changed (Table 1). Before 2006, biologic treatment of soJIA patients in BIKER was in 108 patients (87%) with ETA and in 16 (13%) with ANA. After 2013, only 7 (5%) patients received ETA. Approximately equal numbers received IL-6 inhibition with TOC ($n = 65$; 46.4%) or IL-1 inhibition ($n = 68$; 48.6%).

Baseline patient characteristics

There were marked differences between the cohorts. While patients in the ETA and TOC cohorts had a nearly equal gender distribution, the female: male ratio was about 1: 2 in patients who started an IL-1 inhibitor. Patients in the ETA cohort had the longest disease duration before start of treatment [mean (S.D.): 4.4 (4.0) years], followed by TOC [3.7 (4.3) years], ANA [3.2 (3.8) years] and CAN [2.9 (3.9) years]. The differences were significant only for ETA *vs* ANA ($P = 0.035$) and *vs* CAN ($P = 0.02$). Also fewer patients starting ETA had systemic symptoms ($n = 3$; 14.3%), while the rates were comparable in patients starting TOC, ANA or CAN. The mean number of active joints was significantly different between all cohorts ($P < 0.001$); patients starting ETA had the highest number [mean (S.D.) 8.7 (11)], followed by TOC [5.2 (8.2)], ANA [3.0 (4.5)] and CAN [1.6 (2.5)]. Regarding physician and patient assessed disease activity, patients from the ETA cohort had significantly higher mean values than patients from all other cohorts and TOC treated patients had significantly higher scores than CAN treated patients at baseline (Table 1). cJADAS-10 scores were significantly higher in the ETA cohort [mean (S.D.) 17.5 (7.3)] and significantly lower in the CAN cohort [mean (S.D.) 8.5 (5.5)] compared with the other cohorts. Disability measured by C-HAQ-DI was highest at baseline in ETA treated patients [mean (S.D.) 1.0 (0.82)] with significant differences only between the cohorts with ETA and CAN (Table 1).

Concomitant treatment at baseline was most frequently given in ETA treated patients with conventional synthetic DMARD (94%; in 84% with MTX) and with systemic steroids (84%). The numbers were much lower in the other cohorts (Table 1).

Safety

In all cohorts combined, 464 AE and 92 SAE were reported during exposure to ETA, TOC, ANA or CAN up to 90 days after last dose. The rates for AE and SAE were highest with CAN (AE 108.8/100 EY; SAE 20.3/100 EY) and TOC (AE 99.2/100 EY; SAE 20.9/100 EY), followed by ANA (AE 33.1/100 EY; SAE 6.6/100 EY) and ETA (AE 20.2/100 EY; SAE 3.5/100 EY, Table 2). Patients treated with ETA in combination with systemic steroids had a significantly higher SAE rate (4.9/100 EY *vs* 1.3/100 EY, $P = 0.028$) compared with ETA without systemic steroids. The combination of TOC and systemic steroids resulted in higher AE rates (127.5/100 EY *vs* 79.4/100 EY, $P = 0.002$) and SAE rates (28.4/100 EY *vs* 15.6/100 EY, $P = 0.019$) in comparison with TOC without systemic steroids. Regarding rates of AE, SAE and infections, there were no significant differences whether patients were treated with systemic steroid concomitant to either ANA or CAN. SAE occurred most frequently in the MedDRA system organ class 'infections and infestation' ($n = 24$), 'blood and lymphatic system disorders' ($n = 16$), 'muskulo-skeletal and connective tissue

Table 1 Sociodemographic and clinical characteristics of the patients by bDMARD

	Etanercept ($n = 151$)	Tocilizumab ($n = 109$)	Anakinra ($n = 71$)	Canakinumab ($n = 51$)	*P*-value
Female sex, *n* (%)	76 (50.3)	59 (54.1)	26 (36.6)	19 (37.3)	0.050
Age at JIA onset, mean (S.D.); median, years	5.0 (3.8); 4.1	5.5 (4.4); 4.1	5.2 (4.1); 3.7	5.9 (4.5); 4.4	0.560
Age at bDMARD start, mean (S.D.); median, years	9.4 (5.0); 8.2	9.2 (4.8); 9.6	8.4 (5.0); 7.2	8.8 (4.8); 8.7	0.571
Disease duration at bDMARD start, mean (S.D.); median, years	4.4 (4.0); 3.2	3.7 (4.3); 1.3	3.2 (3.8); 1.1	2.9 (3.9); 0.8	0.075
Number of bDMARDs used before, mean (S.D.); median	1.0 (0.2); 1.0	1.7 (1.1); 1.0	1.6 (0.6); 2.0	2.1 (1.0); 2.0	<0.001
Clinical characteristics at bDMARD start					
Physician assessed disease activity, VAS score, mean (S.D.); median	69.1 (26.6); 74.0	53.9 (31.5); 62.0	51.0 (33.1); 61.0	40.5 (29.9); 41.0	<0.001
CRP, mean (S.D.); median, mg/dL	65.3 (67.1); 44.0	91.6 (182.4); 42.0	87.4 (212.3); 38.5	39.0 (55.5); 10.5	0.135
ESR, mean (S.D.); median, mm/h	48.4 (32.6); 42.0	46.2 (38.1); 40.0	40.2 (31.2); 39.5	26.7 (26.0); 11.0	0.011
Number of active joints, mean (S.D.); median	8.7 (11.0); 4.0	5.2 (8.2); 2.0	3.0 (4.5); 1.0	1.6 (2.5); 0.0	<0.001
cJADAS-10, mean (S.D.); median	17.5 (7.3); 18.1	13.6 (8.0); 13.7	11.7 (8.3); 11.5	8.5 (5.5); 9.1	<0.001
Patient reported outcomes at bDMARD start					
Patient assessed disease activity, VAS score, mean (S.D.); median	53.8 (29.5); 54.5	46.0 (29.8); 51.0	39.1 (31.1); 35.0	33.2 (26.1); 29.0	0.001
C-HAQ total score, mean (S.D.); median	1.00 (0.82); 0.88	0.75 (0.79); 0.63	0.86 (0.94); 0.38	0.62 (0.68); 0.38	0.042
Patient reported pain, VAS score, mean (S.D.); median	42.4 (27.7); 40.0	38.7 (30.3); 37.0	28.3 (29.2); 18.0	31.2 (27.1); 24.0	0.036
Systemic features, *n* (%)					
Any systemic symptom at bDMARD start[a]	3 (14.3)	54 (53.5)	24 (58.5)	22 (47.8)	0.019
Fever	3 (14.3)	45 (44.6)	20 (48.8)	16 (34.8)	0.057
Skin rash	3 (14.3)	37 (36.3)	19 (46.3)	19 (41.3)	0.117
Splenomegaly	1 (4.8)	19 (18.8)	8 (19.5)	6 (13.0)	0.421
Hepatosplenomegaly	1 (4.8)	19 (18.8)	4 (9.8)	1 (2.2)	0.053
Serositis	0 (0.0)	11 (10.9)	4 (9.8)	2 (4.4)	0.456
Generalized lymphadenopathy	0 (0.0)	5 (5.0)	4 (9.8)	4 (8.7)	0.521
Concomitant therapy at bDMARD start, *n* (%)					
Any conventional synthetic DMARD	142 (94.0)	63 (57.8)	38 (53.5)	11 (21.6)	<0.001
Methotrexate	127 (84.1)	60 (55.1)	36 (50.7)	11 (21.6)	<0.001
Ciclosporin A	36 (23.8)	2 (1.8)	3 (4.2)	0 (0.0)	<0.001
Azathioprine	19 (12.6)	3 (2.8)	4 (5.6)	1 (2.0)	0.016
Sulfasalazine	1 (0.7)	1 (0.9)	0 (0.0)	0 (0.0)	0.817
Leflunomide	0 (0.0)	1 (0.9)	2 (2.8)	0 (0.0)	0.355
Hydroxychloroquine	4 (2.7)	0 (0.0)	1 (1.4)	0 (0.0)	0.568
Any systemic steroids	127 (84.1)	79 (72.5)	48 (67.6)	23 (45.1)	<0.001
Year of bDMARD start, *n* (%)					<0.001
≤2006	108 (71.5)	0 (0.0)	16 (22.5)	0 (0.0)	
2007–2012	36 (23.8)	44 (40.4)	28 (39.4)	10 (19.6)	
≥2013	7 (4.6)	65 (59.6)	27 (38.1)	41 (80.4)	

[a]Number of patients with valid information: etanercept $n = 21$, tocilizumab $n = 101$, anakinra $n = 41$, canakinumab $n = 53$.
bDMARD: biologic DMARD; C-HAQ: Childhood Health Assessment Questionnaire; cJADAS-10: clinical Juvenile Arthritis Disease Activity Score 10; VAS: visual analogue scale.

disorder' ($n = 10$) and 'surgical and medical procedures' ($n = 10$).

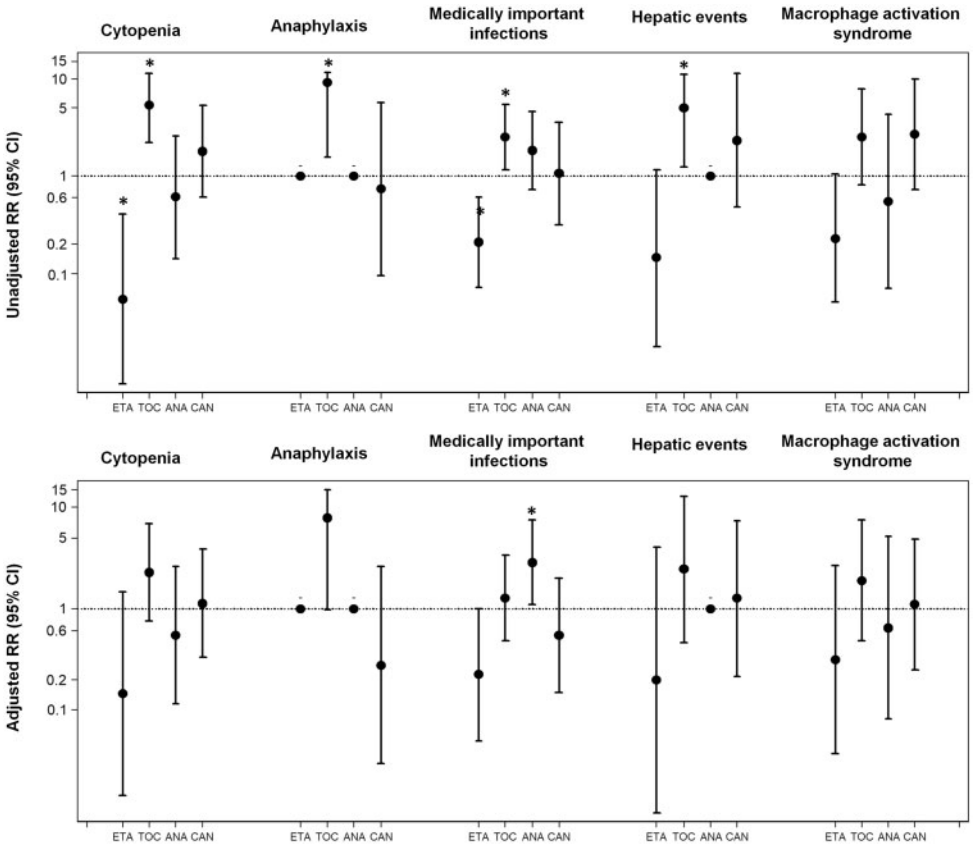
Of 172 infectious AE, 18 occurred in 13 ETA treated patients (4.5/100 EY; risk ratio (RR) = 0.26; 95% CI 0.14, 0.50), 93 infectious events occurred in 37 patients with TOC therapy (38/100 EY; RR = 1.4; 95% CI 0.97, 2.0), 42 were reported in 21 CAN treated patients (44.8/100 EY; RR = 1.49; 95% CI 1.02, 2.23) and 19 were documented in eight patients with ANA (15.7/100 EY, Table 2). When stratified according to concomitant use of systemic steroids, the lower rate in ETA treated patients remained significant only if no concomitant steroids were used at the time of the event (Table 2). A significantly higher rate of infections was reported under a combination therapy of

Table 2 Rates of adverse events, serious adverse events and infectious events by bDMARD

	Etanercept			Tocilizumab			Anakinra			Canakinumab		
	(*n* = 151/EY = 397)			(*n* = 109/EY = 244)			(*n* = 71/EY = 121)			(*n* = 51/EY = 94)		
	Number of patients with AE, *n* (%)	Number of AE AE per 100 EY 95% CI	RR[a] 95%CI *P* value	Number of patients with AE, *n* (%)	Number of AE AE per 100 EY 95% CI	RR[a] 95%CI *P* value	Number of patients with AE, *n* (%)	Number of AE AE per 100 EY 95% CI	RR[a] 95%CI *P* value	Number of patients with AE, *n* (%)	Number of AE AE per 100 EY 95% CI	RR[a] 95%CI *P* value
Any AE	32 (21.2)	80 20.16 15.98, 25.08	**0.47** **0.33, 0.68** **<0.001**	63 (57.8)	242 99.2 87.08, 112.50	**1.33** **1.06, 1.66** **0.014**	15 (21.1)	40 33.05 23.62, 45.02	0.69 0.46, 1.09 0.061	34 (66.7)	102 108.79 88.48, 131.72	**1.41** **1.09, 1.83** **0.009**
Any SAE	9 (6.0)	14 3.53 1.93, 5.92	0.51 0.21, 1.22 0.129	25 (22.9)	51 20.91 15.56, 27.48	1.41 0.86, 2.33 0.178	5 (7.0)	8 6.61 2.85, 13.03	0.70 0.33, 1.48 0.352	13 (25.5)	19 20.26 12.17, 31.56	1.08 0.61, 1.94 0.784
Any infectious AE	13 (8.6)	18 4.54 2.69, 7.17	**0.26** **0.14, 0.50** **<0.001**	37 (33.9)	93 38.1 30.76, 46.69	1.40 0.97, 2.02 0.075	8 (11.3)	19 15.7 9.45, 24.52	0.79 0.48, 1.30 0.360	21 (41.2)	42 44.8 32.20, 60.40	**1.49** **1.02, 2.23** **0.048**
Patients who were treated with a biologic and without systemic steroids (exposure years: etanercept 155; tocilizumab 141; anakinra 60; canakinumab 70)												
Any AE	16 (10.6)	32 20.65 14.12, 29.14	**0.47** **0.28, 0.79** **0.005**	48 (44.0	112 79.4 65.4, 95.58	1.24 0.92, 1.67 0.164	11 (15.5)	19 31.67 19.07, 49.45	0.63 0.39, 1.02 0.060	24 (47.1)	75 107.14 84.27, 134.30	**1.40** **1.00, 1.95** **0.048**
Any SAE	2 (1.3)	2 1.29 0.16, 4.66	0.26 0.05, 1.45 0.124	17 (15.6)	22 15.60 9.78, 23.62	1.63 0.79, 3.33 0.183	3 (4.2)	4 6.67 1.82, 17.07	0.78 0.27, 2.25 0.641	10 (19.6)	13 18.57 9.89, 31.76	0.93 0.43, 2.03 0.855
Any infectious AE	4 (2.6)	8 5.16 2.23, 10.17	**0.20** **0.08, 0.49** **0.001**	27 (24.8)	45 31.91 23.28, 42.70	1.29 0.80, 2.07 0.295	5 (7.0)	8 13.33 5.76, 26.27	0.76 0.36, 1.60 0.469	16 (31.4)	32 45.71 31.27, 64.53	1.57 0.93, 2.66 0.090
Patients who were treated with a biologic in combination with systemic steroids (exposure years: etanercept 242; tocilizumab 103; anakinra 61; canakinumab 24)												
Any AE	22 (14.6)	48 19.83 14.62, 26.30	**0.58** **0.35, 0.97** **0.037**	41 (37.6)	130 127.45 106.49, 151.34	**1.51** **1.06, 2.15** **0.022**	8 (11.3)	21 34.43 21.31, 52.62	0.70 0.43, 1.14 0.155	15 (29.4)	27 112.50 74.14, 163.68	1.05 0.68, 1.62 0.824
Any SAE	7 (4.6)	12 4.96 2.56, 8.66	0.61 0.19, 1.96 0.403	12 (11.0)	29 28.43 19.04, 40.83	1.41 0.67, 2.94 0.367	3 (4.2)	4 6.56 1.79, 16.79	0.72 0.24, 2.15 0.554	5 (9.8)	6 25.00 9.17, 54.41	1.03 0.40, 2.61 0.954
Any infectious AE	9 (6.0)	10 4.13 1.98, 7.60	0.52 0.21, 1.31 0.168	21 (19.3)	48 47.06 34.70, 62.39	1.55 0.86, 2.77 0.141	5 (7.0)	11 18.03 9.00, 32.27	0.88 0.43, 1.80 0.718	7 (13.7)	10 41.67 19.98, 76.63	0.87 0.42, 1.78 0.698

Comparison of each biologic with all events/events under biologic without systemic steroids/events and biologic with systemic steroids against all other analysed biologics in the same constellation. [a]Relative risk adjusted for concomitant use of MTX and steroids, presence of systemic signs, disease duration, cJADAS10, C-HAQ, pain and number of prior treatment cycles with a biologic at start of treatment with etanercept, tocilizumab, anakinra and canakinumab. Bold numbers indicate significance. AE: adverse event; EY: exposure years; RR: relative risk; SAE: serious adverse event.

FIG. 1 Selected AESI comparison of relative risk



RR were calculated for each biologic against all other biologics in the analysis combined. Reported values are unadjusted and adjusted RR. * indicates significance, - RR not estimated by non-occurrence of an event. AESI: adverse events of special interest; ANA: anakinra; CAN: canakinumab; ETA: etanercept; RR: risk ratio; TOC: tocilizumab.

TOC with systemic steroids (47.1/100 EY) compared with TOC without systemic steroids (31.9/100 EY, $P = 0.026$).

The AESI 'medically important infection' comprises serious, medically important and opportunistic infections. Altogether 26 infectious events were allocated to this AESI term with the highest rate in TOC treated patients (5.3/100 EY) with a significant increase in the relative risk compared with the other substances. After adjustment the risk ratio was not significantly elevated (Fig. 1). However, patients treated with ANA had a significantly increased risk after adjustment (5.0/100 EY, RR = 2.82; 95% CI 1.05, 7.60). Patients with CAN had a higher rate of medically important infections (3.2/100 EY), although without reaching statistical significance (Table 3). Apart from two patients with TOC with herpes zoster reactivation, no opportunistic infections have been reported.

Cytopenias were reported in 22 cases in all cohorts, with significantly higher rates in the TOC cohort (6.2/100 EY; RR = 5.37; 95% CI 2.19, 13.17) and higher rates in the CAN cohort (4.3/100 EY). After adjustment none of the treatment groups showed a significantly elevated rate of cytopenias.

Anaphylaxia was seen in TOC treated patients (11 events in nine patients; 4.5/100 EY) and in one patient with CAN (1.1/100 EY). The higher risk in TOC patients was not significant after adjustment.

MAS was reported in all cohorts, with higher frequency in patients with CAN ($n = 3$; 3.2/100 EY) and TOC ($n = 6$; 2.5/100 EY). In the ETA cohort there were two cases of MAS (0.5/100 EY) and in the ANA cohort one case (0.8/100 EY). The differences were not significant.

Hepatic events were one case of hepatic steatosis each in the TOC cohort and in the CAN cohort. Elevation of transaminases with either hyperbilirubinaemia or leading to cessation of medication was documented in three TOC treated patients and in one CAN treated patient. One case of hepatopathy was reported in the ETA cohort. Hepatic events had the highest rate in the TOC cohort with 2.5/100 EY, followed by CAN (2.1/100 EY) and ETA (0.25/100 EY).

Four cases of suspected malignancies were documented in patients who had ever received biologics (0.36/100 PY). A case of myelodysplasia, which was not a confirmed malignancy, and a case of Hodgkin's lymphoma have been described previously [22, 23]. Recently, two other cases were reported: a female patient diagnosed with Hodgkin's lymphoma at the age of

Table 3 Rates of AESI by bDMARD

	Etanercept (*n* = 151/EY = 397)			Tocilizumab (*n* = 109/EY = 244)			Anakinra (*n* = 71/EY = 121)			Canakinumab (*n* = 51/EY = 94)		
	Number of patients with AE, *n* (%)	Number of AE AE per 100 EY 95% CI	RR[a] 95% CI *P*-value	Number of patients with AE, *n* (%)	Number of AE AE per 100 EY 95% CI	RR[a] 95% CI *P*-value	Number of patients with AE, *n* (%)	Number of AE AE per 100 EY 95% CI	RR[a] 95% CI *P*-value	Number of patients with AE, *n* (%)	Number of AE AE per 100 EY 95% CI	RR[a] 95% CI *P*-value
Anaphylaxis	0	0	NE	9 (8.3)	11 4.51 2.25, 8.07	8.28 0.99, 69.09 0.051	0	0	NE	1 (2.0)	1 1.07 0.03, 5.93	0.22 0.02, 2.18 0.194
Inflammatory bowel disease	1 (0.7)	1 0.25 0.01, 1.40	NE	0	0	NE	0	0	NE	0	0	NE
Cytopenia	1 (0.7)	1 0.25 0.01, 1.40	0.14 0.01, 1.39 0.093	11 (10.1)	15 6.15 3.44, 10.14	2.24 0.73, 6.85 0.156	1 (1.4)	2 1.65 0.20, 5.97	0.56 0.12, 2.73 0.474	2 (3.9)	4 4.27 1.16, 10.90	1.17 0.34, 4.08 0.800
Demyelination	1 (0.7)	1 0.25 0.01, 1.40	NE	0 (0.0)	0	NE	0	0	NE	0	0	NE
Hepatic events	1 (0.7)	1 0.25 0.01, 1.40	0.14 0.01, 3.19 0.217	5 (4.6)	6 2.46 0.90, 5.35	2.12 0.37, 12.07 0.398	0	0	NE	2 (3.9)	2 2.13 0.26, 7.69	1.65 0.26, 10.51 0.595
Medically important infections	4 (2.6)	4 1.01 0.27, 2.58	0.23 0.05, 1.03 0.054	11 (10.1)	13 5.33 2.84, 9.11	1.31 0.49, 3.48 0.591	4 (5.6)	6 4.96 1.82, 10.79	**2.82** **1.05, 7.60** **0.041**	3 (5.9)	3 3.2 0.66, 9.33	0.54 0.14, 2.01 0.355
Malignancies	1 (0.7)	1 0.25 0.01, 1.40	1.84 0.01, 7763.91 0.886	1 (0.9)	1 0.41 0.01, 2.28	5.85 0.09, 381.76 0.407	0		NE	0	0	NE
Macrophage activation syndrome	2 (1.3)	2 0.5 0.06, 1.82	0.32 0.04, 2.91 0.315	6 (5.5)	6 2.46 0.90, 5.35	1.91 0.49, 7.46 0.353	1 (1.4)	1 0.83 0.02, 4.60	0.62 0.08, 4.93 0.650	3 (5.9)	3 3.2 0.66, 9.33	1.07 0.24, 4.87 0.930
Depression/ suicidality	0	0	NE	0	0	NE	0	0	NE	1 (2.0)	1 1.07 0.03, 5.93	NE
Thrombosis	0	0	NE	2 (1.8)	2 0.82 0.10, 2.96	NE	0	0	NE	0	0	NE
Uveitis	1 (0.7)	1 0.25 0.01, 1.40	NE	0	0	NE	0	0	NE	0	0	NE
Vasculitis	1 (0.7)	1 0.25 0.01, 1.40	NE	1 (0.9)	1 0.41 0.01, 2.28	1.64 0.05, 54.16 0.781	0	0	NE	0	0	NE

[a]Relative risk adjusted for concomitant use of MTX and steroids at baseline, presence of systemic signs, disease duration, cJADAS-10, C-HAQ, pain and number of prior treatment cycles with a biologic at start of treatment with ETA, TOC, ANA and CAN. AESI with 0 events are not shown; there were no reports about bleeding disorder, gastrointestinal perforation, autoimmune disease other than vasculitis, cardiovascular event, pregnancy, cerebral insult, systemic lupus erythematosus, hepatitis B-reactivation, arterial hypertension, sarcoidosis, serum sickness, pulmonary hypertension or amyloidosis. Bold numbers indicate significance. AE: adverse events; AESI: adverse events of special interest; bDMARD: biologic DMARD; C-HAQ: childhood HAQ; cJADAS-10: clinical juvenile arthritis DAS 10; EY: exposure years; NE: not estimated; RR: risk ratio; SAE: serious adverse event.

9 years had started TOC 1 year earlier after diagnosis of soJIA. The patient also suffers from myotonia congenita Becker. Another female patient was diagnosed with soJIA at the age of 9 months. Upon ANA treatment she developed severe MAS and was treated according to the HLH-protocol with steroids, ciclosporin A and etoposide. At the age of 4 years, she was diagnosed with acute myeloid leukaemia M5. She reached remission after allogeneic stem cell transplantation from a family donor.

Two vasculitic events were documented, one cutaneous panarteritis nodosa in a patient receiving TOC and one case of vasculitic skin changes in the ETA cohort.

Two thrombotic events occurred in the TOC cohort, one case of an arm vein thrombosis after first dose of TOC in a nearly 3-year-old female patient and a case of thrombophlebitis in a 15-year-old patient after 4 years of TOC. A single case of inflammatory bowel disease was reported. At the age of 10 years, a female patient was diagnosed with Crohn's disease after 3 years on ETA. One case of depression was reported in a 15-year-old patient who had been treated with CAN for 11 months before attempting suicide. Demyelination and uveitis was documented in one patient each receiving ETA.

Two deaths occurred, both in patients who had been treated with ETA. One female patient with a very severe course of soJIA and intensive pre-treatment with multiple immunosuppressants succumbed to septic shock and gastrointestinal haemorrhage at the age of 18 years while on treatment with ETA and systemic steroids. Another female patient died at the age of 17 years of cardiac arrest after MAS was diagnosed 2 months earlier and treated with multiple immunosuppressive drugs. ETA had been discontinued 5 months prior to MAS onset. Both events were considered unrelated to ETA treatment.

There was no case of bleeding disorder, gastrointestinal perforation, cardiovascular event, pregnancy, cerebral insult, systemic lupus erythematosus, hepatitis B-reactivation, arterial hypertension, sarcoidosis, serum sickness, pulmonary hypertension or amyloidosis.

Discussion

Severe, persistent soJIA still presents a major therapeutic challenge. Morbidity is influenced by different factors such as disease activity, treatment with systemic steroids, conventional synthetic DMARD and biologics. In order to assess the risk of various, especially rare, AE, large numbers of patients are needed. As soJIA itself is a rare disease this poses a difficult task. The German BIKER registry is one of the largest national registries on the use of biologics in JIA with over 250 patients with soJIA receiving biologic DMARDs. The multinational Pharmachild registry also published data about AE in JIA patients, of which 911 were diagnosed in the systemic-onset category [24]. However, the events were not assigned to JIA categories, whether treatment was ongoing and what kind of DMARD had been used at the time of the events. The American CARRA registry reported data from a comparison of their consensus treatment plans from 30 soJIA patients [17]; numbers of reported AE are low, but this will be a very interesting an important source of safety data related to different therapies for soJIA in the future. The British Society for Paediatric and Adolescent Rheumatology Etanercept Cohort Study (BSPAR-ETN) published data on infectious events in JIA patients, among them 104 patients with soJIA [25]. Most other national registries, such as the Dutch ABC register [12], the US/Canada phase IV, open-label, multicentre registry [26] or the French open-label, multicentre study [13], offer mainly data on JIA patients in general treated with ETA. Direct comparison of AE rates is therefore difficult, because rates are either not published or calculated only for the whole JIA population and rarely for soJIA cohorts specifically.

This analysis focused on the comparison of safety with regard to AE, SAE and selected categories of AE (AESI). The results presented here in part confirm known safety profiles, notably an increased risk for cytopenia and elevation of transaminases in TOC treated patients [7, 8] and an association of intravenous application of TOC and a higher rate of anaphylactic events [8, 17].

Also an overall increased risk of infections and an increased risk for medically important infections in patients with TOC, ANA and CAN was observed in this analysis, which has also been reported in clinical trials with these biologics [6–8, 27]. In cases of TOC, concomitant steroid use might have been a contributing factor. When looking at all infectious events (not only AESI), significantly more infectious events occurred with TOC and systemic steroids compared with treatment with TOC without steroids. This could not be shown for ANA and CAN therapy, although the numbers in the subanalysis according to concomitant steroid use might be too low to reach significance. An analysis of the association between periods of neutropenia and infection rate in both trials with TOC in soJIA showed no increase for rates of serious or non-serious infections during periods of neutropenia [28]. In the BIKER soJIA cohort, there was one report of 3 days of gastroenteritis in a patient receiving TOC, with neutropenia documented 1 year before and 11 months after the event. No infection could be attributed to drug-induced neutropenia.

Compared with the rate of first medically significant infection in JIA patients of 5.5/100 PY published from the BSPAR ETN cohort [25], the rate in ETA treated patients in the BIKER soJIA cohort seems low. As this analysis considered also repeated events and the BSPAR-ETN cohort did not select AE according to JIA category of the patients, the comparison is limited. Comparing with data from the US and Canada from a long-term phase 4 registry, rates of medically important infections of 1.8 and 2.1/100 PY (ETA monotherapy and with MTX) were similar to the rates reported in the BIKER soJIA cohort. In the Dutch ABC registry, soJIA patients, who represented >25% of the whole cohort, had a rate of 1.0/100 PY of serious infections, though

they did not specifically list medically important infections [29].

Patients with JIA are already at greater risk of bacterial infections leading to hospitalization due to their chronic disease, the high disease burden and the high necessity for concomitant treatment with systemic corticosteroids. A study comparing Medicaid data of 8479 JIA patients and 360 489 children diagnosed with attention-deficit hyperactivity disorder [30] found an increased background risk (SIR 2.0) of hospitalized bacterial infection for JIA patients not currently treated with MTX or TNFi. However, the risk did not increase with MTX or TNFi treatment, but a significant increase was seen with the use of glucocorticosteroids. Patients with soJIA were not analysed separately. There are indications that diagnosis of soJIA is associated with a higher incidence of infection than other JIA categories [31, 32]. Younger age, the disease itself with systemic inflammation and a high ratio of patients receiving systemic steroids might all be contributing factors. In the BSPAR-ETN, diagnosis of soJIA determined as a univariate predictor for medically significant as well as serious infections [25]. A comparison of patients treated with ANA and soJIA patients treated with MTX using Medicaid data calculated an increased, but not significant, risk ratio for ANA users regarding hospitalized infections [33]. Altogether infection rates have to be interpreted with care. Apart from herpes zoster, no opportunistic infections were observed in the BIKER soJIA cohort. In a large multinational retrospective registry, the Pharmachild registry, 27 cases of tuberculosis were reported [24]. They did not stratify their AESI according to therapy or JIA category, and thus comparability is limited. Different incidence rates in the various countries and a very low risk of tuberculosis infection in Germany could explain the lower rate in BIKER. A validated test for tuberculosis before start of biologic treatment is recommended and routinely performed in Germany and may also contribute to the low incidence of tuberculosis in BIKER.

In total, 12 MAS events were reported to BIKER. There are no certain estimates of the incidence of MAS in soJIA; there are reports of ~10% [10], but occult prevalence might be as high as 30% [34]. MAS accounts for a significant proportion of morbidity and mortality in soJIA [10]. Infections are the most common trigger, and it is reported also in patients receiving successful treatment [35]. The occurrence of MAS has been described with all the analysed biologic therapies [35–37]; it has also been reported in patients treated in the CARRA study with TOC and ANA [17]. None of these therapies seems to be able to protect fully against MAS. Even with ANA, which has been reported as an effective treatment for MAS in several case series, MAS cases have been reported, though there might be a dose-related issue [36]. The one MAS reported in the ANA cohort developed despite a relatively high ANA dose of 5 mg/kg body weight. Altogether, the MAS rates were comparably low in the BIKER cohort, also when analysed according to treatment, though there might have been undetected cases. Interestingly, there was a relatively low rate in ETA treated patients. There are single case reports of successful treatment of MAS with ETA [38], but also reports about MAS cases potentially triggered by ETA [37]. It has to be considered that patients with ETA had a longer duration of their disease before starting ETA than the other cohorts, but MAS has been described even years after onset of soJIA [10]. Another influencing factor might be that most ETA treatment courses for soJIA were documented before 2006. It is possible that MAS is diagnosed more frequently in recent years due to an increasing awareness among physicians.

Two death were reported in BIKER, both in this soJIA cohort. In the Enhanced Drug Safety Surveillance Project in the USA [39], in JIA patients regardless of JIA category or treatment, a mortality rate of 0.03/100 PY was observed. Five of the seven reported deaths occurred in soJIA patients, the majority given as MAS related. One death in the BIKER cohort was also MAS related. The mortality rate in the BIKER ETA cohort (all JIA patients) was calculated as 0.024/100 PY. Also, in the Dutch registry three patients with soJIA died, one of them due to MAS, resulting in a high mortality rate of 0.96/100 PY [29]. As the rates from BIKER and the Dutch registry are in ETA treated patients only, they cannot be compared with the Enhanced Drug Safety Surveillance Project mortality rate.

Four suspected malignancies have been reported to the BIKER registry in soJIA patients, two in patients receiving biologics at the time of diagnosis of malignancy. Both were Hodgkin's lymphoma, but occurred in patients with different groups of biologics (TNFi and IL-6 inhibitor). The background risk for malignancies in JIA patients might be higher than in the general population. In a nationwide cohort study in the USA, Beukelman *et al.* found a 3-fold increased risk for highly probable malignancies in patients with JIA (all categories) compared with children with attention-deficit hyperactivity disorder. Treatment with either MTX or TNFi did not appear significantly associated with the development of malignancy [40]. As soJIA differs from other JIA categories and has a strong autoinflammatory component, it cannot be deduced that the malignancy risk would be similar in soJIA. Due to the low incidence rates of soJIA, there are no reliable numbers regarding the risk for malignant disease.

A single case showed cutaneous panarteritis nodosa and the responsible physician was encouraged to test this patient for deficiency of adenosine demaninase-2, but the result has not been reported to BIKER yet.

Depression and or suicidality was documented with a relatively low rate in this cohort with only one report in 260 patients. Data in patients with JIA regardless of subcategory report an incidence of depression as high as 15% [41]. This might correlate with younger age in soJIA patients [42]. Depressive disorders have a lower incidence in younger children and are more difficult to

diagnose. Depressive symptoms are also often associated with female gender. Unlike with most of the other JIA categories soJIA has an equal gender distribution [46].

This analysis has a number of limitations. The treatment cohorts differ in several aspects, and thus higher rates of events observed cannot be attributed to a higher risk of the drug itself. Especially ETA treated patients had a longer disease duration, more joint involvement and higher disability scores, but also less systemic activity. Patients with a longer disease course of soJIA quite often have persistent articular disease with systemic features disappearing. Thus, these patients were selected to receive a TNF inhibitor to treat articular manifestation of their disease resulting in a potential channelling bias. Also concomitant treatment did differ between the cohorts. Therefore, the analysis was adjusted for disease activity and concomitant treatment. The number of AE, SAE and AESI were small despite the large number of patients with soJIA in our analysis, limiting statistical power in the comparison of the four treatments. With the more recent treatments inhibiting IL-1 or IL-6, these days patients are rarely treated with TNFi. IL-1 inhibition given early in the disease course seems to yield better treatment response and long-lasting remission [14, 15]. Duration of treatment with these biologics was lower in the BIKER cohort. Awareness for AE and the frequency of clinical and laboratory controls are supposedly higher at the start of a therapy. This might lead to under-detection or under-reporting of AE in patients receiving long-term treatment. Patients in a registry are unselected and not treated according to a protocol and medications can be changed. We used a 90-day risk window for AE after discontinuation of the biologic as an established approach in paediatric and adult rheumatology. However, this flat-rate approach did not consider the different half-life of each biologic. In particular, this approach may be problematic for canakinumab. However, no AE was reported after discontinuation of canakinumab. A strength of this analysis is the real-life setting and the mean follow-up period of 4.3 years. Only with a registry documenting the routine clinical care can a relevant quantity of patient years be accumulated so that rare events can be captured and rates can be calculated. Altogether, the tolerability of the analysed biologics seems acceptable. Nevertheless, the data are valuable and provide enhanced knowledge on safety of different biologics for physicians treating soJIA patients. More data are needed to estimate the influence of different biologics or the underlying disease on the occurrence of certain events.

Conclusion

Long-term surveillance of biologic therapies in JIA is an important task. In rare diseases such as soJIA this can be achieved with the use of registries. Comparing the rates of AESI between different biologic treatments showed an acceptable safety profile in all treatment cohorts.

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