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FRI0548

EFFICACY AND SAFETY OF TOCILIZUMAB IN SYSTEMIC AND POLYARTICULAR JUVENILE IDIOPATHIC ARTHRITIS – DATA OF THE BIKER REGISTRY

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Background: Since 2011 Tocilizumab is approved for systemic juvenile idiopathic arthritis (JIA) and since 2013 for polyarticular JIA

Objectives: To describe efficacy and safety of Tocilizumab in clinical practice in polyarticular (pJIA) and systemic JIA (sJIA) patients using the German Biologics registry (BiKeR)

Methods: Baseline demographics and disease activity parameters have been documented. Efficacy was determined using the JADAS10 prospectively. Safety assessments were based on adverse events reports (AE) processed according to MedDRA

Results: Until October 1, 2018, 345 JIA patients treated with Tocilizumab were registered, representing 635 patient-years (PY) of observation. The cohort treated with Tocilizumab had experienced disease duration of 5.5 +/-4.3 years (mean+/-SD) for sJIA and 5.9+/-4.1 years for pJIA. sJIA/pJIA patients received pretreatment with MTX 72%/96%, Anakinra 23%/1%, Adalimumab 4%/60%, Etanercept 30%/69%, Canakinumab 2%/0%. Concomitantly, sJIA/pJIA patients received NSAIDs 64%/57%, systemic steroids 72%/35%, MTX 55%/54%, other DMARDs 4%/8%. At last follow-up, 63%/60%/51%/43% of sJIA and 56%/49%/40%/30% of pJIA patients reached JIAACR30/50/70/90 criteria. After 2 years of treatment JADAS remission was reached by 50%/43% and JADAS minimal disease activity by 67%/67%.

586 AE were reported during exposure plus 90 days of observation. The rate was significantly higher in sJIA (104/100PY [95% CI 92-119]) than in pJIA patients (79 [79-90]; RR 1.3; p=0.003). 75 qualified as serious AE (SAE) with a higher rate in sJIA (22[16-29] vs. 8 [5-12], RR 2.6; p<0.001). The most frequent AE in the sJIA/pJIA cohort were grouped in the MedDRA SOC infections and infestations (n=92/76). Compared to pJIA, rates were significantly higher in sJIA patients for blood and lymphatic (RR 2.4; p=0.019), immune system (RR 2.6; p=0.04), infections & infestations (RR 1.7, p<0.001) and nervous system disorder (RR 2.6, p=0.012) and lower for general and administration site (RR 0.4; p=0.023). 169 patients (49%) discontinued treatment, 17% due to remission, 22% due to lack of efficacy and 9% because of intolerance.

Conclusion: The analysis adds to the established safety profile of tocilizumab in paediatric patients with systemic & polyJIA. Differences were noted between pJIA and sJIA cohorts, the latter with higher rates of total number of adverse events, serious AE, infections and cytopenias, probably due to higher doses or shorter application intervals. No new safety signals specific to the paediatric population were identified in this large cohort of JIA patients.

	sJIA (n=109)	pJIA (n=239)	RR/p
All AE (rate[95%CI])	234(104[92-119])	252 (79[70-90])	0.76/0.003
SAE	49 (22[16-29])	26 (8[5-12])	0.38/<0.001
blood & lymphatic system ¹	20 (9[6-14])	12(4[2-7])	0.42/0.019
gastrointestinal disorders	13 (6[3-10])	30(9[7-14])	n.s.
general disorder & administration site condition ²	9 (4[2-8])	30 (9[7-14])	2.4/0.023
immune system disorders ³	13 (6[3-10])	7 (2[1-5])	0.38/0.040
infections and infestations ⁴	92 (41[33-50])	76 (24[19-30])	0.59/<0.001
injury, poisoning and procedural complications	7 (3[1-7])	10 (3[2-6])	n.s.
neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0[0-3])	2(1[0-3])	n.s.
nervous system disorders ⁵	20 (9[6-14])	11(3[2-6])	0.39/0.012
skin and subcutaneous tissue disorders	11(5[3-9])	11(3[2-6])	n.s.

MedDRA-SOC: Rates are outlined as number during exposure + 90 days follow up, censored if an alternative biologic has been applied. 1 MAS, neutrophil, thrombocytopenia; 2 nausea, aphthosis; 3 allergic reactions; 4 viral and bacterial infections; 5 seizures

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sJIA

polyJIA

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SARILUMAB, A HUMAN MONOCLONAL ANTIBODY TO THE INTERLEUKIN-6 (IL-6) RECEPTOR, IN POLYARTICULAR-COURSE JUVENILE IDIOPATHIC ARTHRITIS (PCJIA): A 12-WEEK MULTINATIONAL OPEN-LABEL DOSE-FINDING STUDY

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Background: Sarilumab blocks IL-6 from binding to membrane and soluble IL-6 receptor-α. Sarilumab is approved for adults with rheumatoid arthritis (RA) and is being investigated in a Phase 2 trial (NCT02776735)

in 2–17-year-old patients (pts) with pcJIA, comprising rheumatoid-factor (RF)-positive and RF-negative polyarticular and extended oligoarticular JIA. **Objectives:** Evaluation of pharmacokinetics (PK), pharmacodynamics (PD), safety, and efficacy of 3 subcutaneous (SC) sarilumab doses in pcJIA.

Methods: A 12-week dose-finding study was performed to identify an appropriate sarilumab dose for use in the pcJIA population. Pts were divided by body weight into 2 groups: A (30–60 kg) and B (10–<30 kg), and received sequential ascending doses of sarilumab, Dose 1 (Group A/B): 2.0/2.5 mg/kg q2w; Dose 2 (Group A/B): 3/4 mg/kg q2w; and Dose 3 (Group A/B): 2.0/2.5 mg/kg qw. pcJIA doses were targeted to achieve similar exposure to adult RA doses (150 mg q2w, 200 mg q2w, and 150 mg qw). Primary outcome was PK; secondary outcomes were safety, PD, and efficacy of sarilumab.

Results: 42 pts enrolled (20/22 in Groups A/B); mean age was 13.0/5.2 years. At baseline, mean pcJIA duration, number of active joints, and JADAS27-CRP were 4.6/1.7 years, 17.2/11.0, and 22.2/19.1, in Groups A/B, respectively. As in adult pts, sarilumab exhibited nonlinear PK with target-mediated drug disposition (TMDD). Following repeated SC administrations, exposure increased in a greater than dose-proportional manner and accumulated 1.9–4.5-fold over 12 weeks. Sarilumab exposure was similar in both weight groups for each dose (Figure), and comparable to corresponding adult doses. Treatment-emergent adverse events (AEs) were reported in 36/42 (85.7%) pts (comparable across dose and weight groups); infections (28/42, 66.7%) were the most frequently reported AE. 12 grade 3/4 neutropenias were identified, mostly in Dose 3 (n=6) and in Group B (n=8). None was associated with infection; all resolved in a few days. Overall, 4 pts discontinued due to neutropenia and 1 due to alanine aminotransferase increase. There were no serious AEs, no cases of GI perforation, and no deaths. By Week 12, as observed while on-treatment: all pts attained JIA ACR30; 50%, 62%, and 100% of pts attained JIA ACR70 with Doses 1, 2, and 3, respectively; JADAS27-CRP mean % changes from baseline in Doses 1, 2, and 3 were -74.6%, -73.1%, and -87.9%, respectively.

Figure. Mean (CV%) individual sarilumab exposure, following first SC dose, and after repeated SC administration at Weeks 10–12 or Weeks 11–12, in patients with pcJIAFirst

pcJIA treatment		First SC administration			Repeated SC administration (Weeks 10–12 or Weeks 11–12)		
Patient weight group	Sarilumab dose	N	C _{0-12h} , mg/L (CV%)	AUC _{0-12h} , day mg/L (CV%)	N	C _{0-12h} , mg/L (CV%)	AUC _{0-12h} , day mg/L (CV%)
10–<30 kg (Group B)	2.5 mg/kg q2w	6	0.54 (48)	63 (30)	5	1.83 (101)	118 (37)
	4.0 mg/kg q2w	7	3.77 (43)	167 (26)	7	11.90 (41)	310 (26)
	2.5 mg/kg qw	9	5.22 (39)	45 (36)	5	25.10 (29)	203 (25)
30–60 kg (Group A)	2.0 mg/kg q2w	7	0.63 (63)	53 (46)	5	1.99 (86)	114 (18)
	3.0 mg/kg q2w	7	1.84 (69)	123 (24)	6	8.46 (68)	269 (34)
	2.0 mg/kg qw	6	8.07 (32)	61 (22)	6	30.40 (28)	250 (24)

AUC, area under the serum concentration versus time curve, calculated using trapezoidal method during a dose interval; C_{0-12h}, serum concentration observed before treatment administration during repeated dosing; CV, coefficient of variance; N, number of patients; pcJIA, polyarticular-course juvenile idiopathic arthritis; qw, every week; q2w, every 2 weeks; SC, subcutaneous.
Dose interval (q) was 2 weeks for q2w, or 1 week for qw regimen.

Conclusion: Sarilumab exhibited nonlinear PK with TMDD. Doses tested in pcJIA yielded similar exposure in both weight groups and were comparable to equivalent doses in adults with RA. All dose regimens proved effective for decreasing disease activity. Safety profile was consistent with class effects; higher incidences of neutropenia were observed with Dose 3, and in pts weighing 10–<30 kg.

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JIA DISEASE ACTIVITY OUTCOMES ACROSS A MULTI-CENTER COHORT: ANALYSIS OF THE PEDIATRIC RHEUMATOLOGY CARE AND OUTCOMES IMPROVEMENT NETWORK (PR-COIN) REGISTRY

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Background: Clinical remission is widely accepted as the primary target outcome for juvenile idiopathic arthritis (JIA). PR-COIN is a quality improvement collaborative that serves as a sample of pediatric rheumatology centers in North America. By measuring disease activity in practice using the ACR provisional criteria for Clinical Inactive Disease (CID), variation in patient outcomes has been previously observed between centers. **Objectives:** The objective of this study was to evaluate differences in patient-level factors that may be driving center-level variation in JIA outcomes.

Methods: This study used cross-sectional data provided by PR-COIN that was collected by PR-COIN centers from March 2015 to May 2016. For each patient, sociodemographic, clinical, patient-reported, disease activity, and medication variables were extracted from the most recent encounter. Patients with disease duration less than 9 months were excluded. Patients were grouped by CID status (inactive vs active disease) and then compared using descriptive statistics, chi-square for categorical variables, and independent t-tests for continuous variables. Missing data were excluded with each analysis. Analyses were performed using R software.

Results: There were 2751 patients eligible for analysis from 14 centers, with 33 to 394 patients per center. We identified 1249 patients with inactive disease (47%) and 1428 patients with active disease (53%). Patients with inactive disease were younger (12 vs 13 years), more likely to have persistent oligoarticular subtype (33% vs 23%), and less likely to have enthesitis related arthritis (9% vs 14%). Patients with active disease had higher patient-reported measures of global assessment of disease activity, pain, and functional disability, as well as disease activity measures per definition. More medication usage was observed in patients with active disease compared to inactive disease across multiple categories, including both non-biologic DMARDs (45% vs. 32%) and biologic DMARDs (48% vs 35%).

Conclusion: This study demonstrates differences in sociodemographic, clinical, and medication factors between patients with inactive and active JIA. Further analysis is needed to adjust center-level measures of JIA disease activity using the observed differences in patient case-mix. By using population data to identify predictors of inactive disease in JIA, there is potential to develop and implement targeted clinical interventions to directly impact care and improve outcomes.

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