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ACR Concurrent Abstract Session
Pediatric Rheumatology - Clinical and Therapeutic Aspects: Juvenile Idiopathic Arthritis
Sunday, November 16, 2014, 4:30 PM–6:00 PM

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A Multinational Study of the Epidemiology, Treatment and Outcome of Childhood Arthritis Preliminary Data from 6,940 Patients. Alessandro Consolaro[1], Amita Aggarwal[2], Troels Herlin[3], Olga Vougiouka[4], Rubén Burgos-Vargas[5], Ilonka Orban[6], Nahid Shafaie[7], Maria Trachana[8], Lidia Rutkowska-Sak[9], Ingrida Rumba-Rozenfelde[10], Dimitrina Mihaylova[11], Alberto Martini[1] and Angelo Ravelli[12]. [1]Istituto Giannina Gaslini, Genova, Italy, [2]Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, India, [3]Aarhus University Hospital, Aarhus, Denmark, [4]P. A. Kyriakou Childrens Hospital of Athens University, Athens, Greece, [5]Hospital General de Mexico, Universidad Nacional Autonoma de Mexico, Mexico City, Mexico, [6]National Institute of Rheumatology and Physiotherapy, Budapest, Hungary, [7]Tehran University of Medical Sciences, Tehran, Iran, [8]Aristotle University, Thessaloniki, Greece, [9]Institute of Rheumatology, Warsaw, Poland, [10]University of Latvia, Riga, Latvia, [11]University Children Hospital, Sofia, Bulgaria, [12]Istituto Giannina Gaslini and University of Genova, Genova, Italy.

Background/Purpose: The epidemiology of juvenile idiopathic arthritis (JIA) is known to be variable worldwide and the therapeutic approach to JIA is not standardized. Moreover, the availability of the novel and costly biologic medications is not uniform throughout the world, with possible significant impact on disease prognosis. The EPOCA study is aimed to obtain information on the frequency of JIA subtypes in different geographic areas, the therapeutic approaches adopted, and the disease status of children with JIA currently followed worldwide.

Methods: So far, 124 centers in 55 countries have agreed to participate in the study. Participation in the study was proposed to the pediatric rheumatology center of all countries belonging to the Pediatric Rheumatology International Trials Organization (PRINTO), and to several centers in the US and Canada. Each centre was asked to enroll 100 consecutive JIA patients or, if less than 100, all consecutive patients seen within 6 months. Each patient received a retrospective and cross-sectional assessment. Parent- and child-reported outcomes were recorded through the administration of the Juvenile Arthritis Multidimensional Assessment Report (JAMAR). Participating countries were grouped into 6 geographic areas.

Results: Currently, 6,940 patients from 41 countries have been entered in the web database. Comparison of data from the different geographic areas is presented in the table.

	Africa N = 79	Asia N = 726	Eastern Europe N = 2171	Latin America N = 795	North America N = 243	Western Europe N = 2845
JIA onset age, yrs, median (IQR)	5.7 (2.8; 10)	5.9 (2.9; 9.5)	6.3 (2.8; 10.4)	6.6 (3.5; 10.3)	7.5 (3.2; 11)	4 (2; 8.7)
Systemic arthritis, N (%)	11 (13.9)	174 (24)	165 (7.6)	143 (18)	16 (4.9)	202 (7.1)
Oligoarthritis, N (%)	25 (31.6)	256 (35.3)	958 (44.1)	247 (31.1)	103 (31.8)	1398 (49.1)
Enthesitis related arthritis, N (%)	3 (3.8)	92 (12.7)	248 (11.4)	74 (9.3)	35 (10.8)	253 (8.9)
Uveitis, N (%)	4 (5.1)	40 (5.5)	232 (10.7)	51 (6.4)	38 (11.7)	495 (17.4)
JADAS10, median (IQR)	5 (1.5; 10)	3.5 (0.5; 10)	5 (1; 10.6)	3.5 (0; 10.8)	2 (0; 5.5)	2 (0; 6.3)
Inactive disease, N (%)	13 (16.5)	237 (32.6)	454 (20.9)	268 (33.7)	114 (35.2)	1070 (37.6)
JADI articular > 0, N (%)	27 (34.2)	136 (18.7)	531 (24.5)	257 (32.3)	60 (18.5)	352 (12.4)
Treated with biologics, N (%)	27 (34.2)	134 (18.5)	637 (29.3)	273 (34.3)	178 (54.9)	1067 (37.5)

Conclusion: Patients seen in Western Europe have a younger age at onset and a greater prevalence of uveitis. Systemic arthritis is more common in Asian patients, whereas enthesitis related arthritis is less frequent in African patients. Children from Africa and Eastern Europe have a higher level of disease activity and a lower frequency of inactive disease, and African and Latin American patients have a greater prevalence of articular damage. Biologic medication are administered more frequently in North America and less commonly in Asia.

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Antibiotic Exposure and the Development of Juvenile Idiopathic Arthritis: A Population-Based Case-Control Study. Daniel B. Horton[1], Frank I. Scott IV[2], Kevin Haynes[1], Mary E. Putt[1], Carlos D. Rose[3], James D. Lewis[1] and Brian L. Strom[4]. [1]Center for Clinical Epidemiology and Biostatistics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, [2]Division of Gastroenterology, Hospital of the University of Pennsylvania, Philadelphia, PA, [3]Division of Rheumatology, Nemours A.I. duPont Hospital for Children, Thomas Jefferson University, Wilmington, DE, [4]Rutgers Biomedical and Health Sciences, Newark, NJ.

Background/Purpose: Dysregulation of the human microbiome has been implicated in the development of several autoimmune diseases, including rheumatoid arthritis and inflammatory bowel disease (IBD). Moreover, antibiotic exposure has been linked with the development of IBD in children. This study aimed to determine whether early antibiotic exposure increases the risk of incident juvenile idiopathic arthritis (JIA) in a general pediatric population.

Methods: A nested case-control study was conducted using The Health Improvement Network, a United Kingdom population-based medical records database with comprehensive diagnostic and outpatient prescription data. Children with incident JIA diagnosed before age 16 were identified by validated diagnostic codes (positive predictive value 86%). Age- and sex-matched control subjects were randomly selected with incidence density sampling in a 10:1 ratio from general practices taking care of at least 1 child diagnosed with JIA. Eligible subjects needed to be registered within 3 months of their birthdate. Individuals with prior IBD, immunodeficiency, autoimmune connective tissue disease, or vasculitis were excluded. The association between antibiotic prescriptions and JIA diagnosis was determined by conditional logistic regression.

Results: There were 153 children diagnosed with JIA in the study population (table 1). Any antibiotic exposure was associated with an increased risk of developing JIA after adjusting for confounders (adjusted OR 2.6, 95% CI 1.5,4.6) (table 2). This risk increased with the number of prescriptions in a dose-dependent manner. These results did not significantly change when adjusting for the number or type of infections. Age of exposure did not significantly modify this association. The relationship between antibiotics and incident JIA was similar across different antibiotic classes, although use of non-bacterial antimicrobial agents (e.g., antifungal, antiviral) was not associated with JIA. In sensitivity analyses excluding data up to 12 months before the index date, the association between antibiotics and incident JIA did not substantively change.

Conclusion: Antibiotic exposure was associated with an increased incidence of JIA in a dose-dependent fashion in a large pediatric population. This study implicates a role for antibiotic exposure in disease pathogenesis, perhaps mediated through alteration in the microbiome.

Table 1 Subject characteristics

	Cases n = 153	Controls n = 1530	Total n = 1683	p value
Female	96 (63)	960 (63)	1056 (63)	1.00
Age category	107 (70)	1070 (70)	1177 (70)	1.00
1-5 years	36 (23)	360 (23)	396 (23)	
6-10 years	10 (7)	100 (7)	110 (7)	
11-15 years				
Low socioeconomic status	23 (15)	216 (14)	239 (14)	0.65
Personal autoimmune disease	5 (3)	2 (0.1)	7 (0.4)	<0.001
Psoriasis	3 (2)	2 (0.1)	5 (0.3)	
Type 1 diabetes	1 (0.7)	0	1 (<0.1)	
Thyroid disease	1 (0.7)	0	1 (<0.1)	
Uveitis	1 (0.7)	0	1 (<0.1)	
Hospitalization	44 (29)	195 (13)	239 (14)	<0.001
Any infection	142 (93)	1313 (86)	1455 (86)	0.02
Upper respiratory	125 (82)	1138 (74)	1263 (75)	
Lower respiratory	37 (24)	394 (26)	431 (26)	
Gastrointestinal	30 (20)	253 (17)	283 (17)	
Skin and soft tissue	35 (23)	296 (19)	331 (20)	
Urinary tract	7 (5)	63 (4)	70 (4)	
Bone and joint	0	0	0	
Other	83 (54)	865 (57)	948 (56)	
Total infections, median (IQR)	3 (1,4)	2 (1,4)	2 (1,4)	<0.001
Any antibiotic exposure	134 (88)	1157 (76)	1291 (77)	<0.001
Antianaerobic	127 (83)	1109 (72)	1236 (73)	0.004

Not antianaerobic	65 (42)	475 (31)	540 (32)	0.002
Number of antibiotic courses received	19 (12)			
Unexposed	40 (26)	373 (24)	392 (23)	
1-2 courses	46 (30)	500 (33)	540 (32)	
3-5 courses	48 (31)	345 (23)	391 (23)	
More than 5 courses		312 (20)	360 (21)	
*Other antimicrobial exposure, any	45 (29)	405 (26)	450 (27)	0.43
Maternal autoimmune disease	21 (14)	116 (8)	137 (8)	0.02
Prenatal antibiotic exposure	47 (31)	512 (33)	559 (33)	0.51

Legend. IQR interquartile range. All statistics are expressed as n (%) unless otherwise stated. All p values were obtained from univariable conditional logistic regression models.
*Other antimicrobial agents, including antifungal, antiviral, and antimycobacterial drugs.

Table 2 Multivariable models

Exposure associated with JIA	Odds ratio	95% CI	p value
Any antibiotic	2.6	1.5,4.6	0.001
Any antibiotic, by dose category			
Unexposed (reference)	2.0	1.1,3.7	0.03
1–2 courses	3.1	1.6,5.8	<0.001
3–5 courses	3.8	1.9,7.3	<0.001
More than 5 courses			

Legend. Final models adjusted for matching, personal autoimmune disease (any), hospitalization, and maternal autoimmune disease (any).

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An Exploratory Analysis of Predictors of Response from 12-Weeks of Canakinumab Therapy in Patients with Active Systemic Juvenile Idiopathic Arthritis. Hermine I. Brunner[1], Nicola Ruperto[2], Isabelle Koné-Paut[2], Bo Magnusson[2], Seza Ozen[2], Flavio Sztajnbok[2], Jordi Anton[2], Judith Barash[2], Reinhard Berner[2], Fabrizia Corona[2], Karine Lheritier[3], Corine Gaillez[3], Alberto Martini[2] and Daniel Lovell[1]. [1]PRCSG, Cincinnati, OH, [2]PRINTO-Istituto Gaslini, Genova, Italy, [3]Novartis Pharma AG, Basel, Switzerland.

Background/Purpose: Systemic juvenile idiopathic arthritis (SJIA), an interleukin-1β (IL-1β)-mediated autoinflammatory disease, is characterized by recurrent flares of active disease. Canakinumab (CAN), a selective, human, anti- interleukin-1β monoclonal antibody, has been shown to be efficacious in the treatment of SJIA (Ruperto et al. N Engl J Med 2012). The present study aimed to explore baseline demographics and clinical characteristics that are most predictive of response to CAN in CAN-naïve SJIA patients during the initial 12 weeks of therapy.

Methods: Data from 3 trials were pooled for this analysis. CAN-naïve patients (pts; n=178) aged 2–19 years with active SJIA were enrolled and received sc CAN 4 mg/kg/month; Predictors of response (according to aACR* 30, 70, and Inactive Disease [ID]) at Days (D) 15, 29, 57 and 85 were explored using univariate and multivariate logistic regression analyses. The candidate predictors (categorical variables) of CAN-response considered were: Age group, Gender, Prior NSAIDs (no/yes), Prior MTX (no/yes), Steroids (0, >0 – ≤0.4; > 0.4 mg/kg/day), Number of Active Joints (≤10, 11-≤20, >20) and Joints with Limitation of Motion (≤10, 11-≤20, >20), CRP (elevated/normal) at baseline and at D15. All candidate predictors with p<0.1 in univariate analyses were included in the multivariate analysis. *ACR response plus absence of fever.

Results: By Week 2 there was substantial clinical benefit with 102 pts (57%) and 36 pts (20%) achieving aACR70 and ID, respectively; by Week 12, 108 pts (61%) had aACR70 and 50 pts (28%) ID. The multivariate analysis indicated that normal CRP at D15 is the only predictor significant (all p<0.05) for ID at all time-points (Table).

Table: Inactive Disease - Multivariate logistic regression analysis on 12-week data

	Odds Ratio (95% CI)			
Variable*	Day 15	Day 29	Day 57	Day 85
CRP at Day 15 (elevated vs normal)	**0.20 (0.07, 0.55)**	**0.14 (0.04, 0.41)**	**0.26 (0.10, 0.66)**	**0.31 (0.12, 0.82)**
Number of active joints (11-≤20 vs. ≤10)	0.22 (0.03, 1.66)	0.55 (0.09, 3.41)	**0.17 (0.031, 0.97)**	0.37 (0.06, 2.10)
Number of active joints (≤10 vs. >20)	2.56 (0.12, 55.39)	1.53 (0.06, 37.44)	**16.10 (1.00, 258.12)**	25.41 (1.60, 404.61)
Prior NSAID treatment (no vs. yes)	2.01 (0.71, 5.71)	**9.33 (2.44, 35.68)**	**3.10 (1.03, 9.31)**	**5.31 (1.66, 17.05)**
Steroid Level (0 vs. >0.4 mg/kg/day)	5.48 (0.97, 31.01)	**8.89 (1.26, 62.64)**	2.98 (0.51, 17.46)	**11.16 (1.72, 72.34)**
Steroid Level (>0.4 vs >0-≤0.4 mg/kg/day)	0.32 (0.08, 1.29)	0.41 (0.09, 1.82)	0.81 (0.25, 2.60)	**0.13 (0.03, 0.57)**
Prior MTX treatment (no vs. yes)	1.94 (0.75, 5.00)	2.78 (0.93, 8.33)	**2.79 (1.04, 7.51)**	1.77 (0.65, 4.83)
Prior anti-TNFs treatment (no vs. yes)	1.83 (0.52, 6.49)	3.62 (0.77, 17.00)	2.01 (0.63, 6.38)	**3.64 (1.04, 12.77)**

Values in bold are significant; *Significant in at least one time point

Conclusion: This exploratory analysis suggests that canakinumab-naïve patients with normal CRP (i.e. ≤10 mg/l) at Day 15, lower baseline steroid doses, low number of active joints, no prior NSAID use are most likely to achieve inactive disease up to 12 weeks.

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Response to Canakinumab Treatment Is Maintained in Systemic Juvenile Idiopathic Arthritis Patients. N.M. Wulffraat[1], N. Ruperto[2], H.I. Brunner[3], S. Oliveira[2], Y. Uziel[2], K. Nistala[2], R. Cimaz[2], M. Ferrandiz[2], B. Flato[2], M.L. Gamir[2], I. Koné-Paut[2], C. Gaillez[4], K. Lheritier[4], K. Abrams[5], A. Martini[2] and D.J. Lovell[3]. [1]UMC Utrecht, Utrecht, Netherlands, [2]PRINTO-Istituto Gaslini, Genova, Italy, [3]PRCSG, Cincinnati, OH, [4]Novartis Pharma AG, Basel, Switzerland, [5]Novartis Pharmaceuticals Corporation, East Hanover, NJ.

Background/Purpose: Canakinumab, a selective, human, anti-interleukin (IL) −1β monoclonal antibody, is approved for the treatment of systemic juvenile idiopathic arthritis (SJIA) patients (≥ 2 years old). SJIA is an IL-1β-mediated autoinflammatory disease, which is characterized by recurrent flares of active disease. Canakinumab treatment in patients with SJIA, allows for successful steroid dose reduction/discontinuation and reduces risk to experience a flare. [1] We evaluated the maintenance of efficacy with continued canakinumab treatment in SJIA patients during the blinded randomized treatment withdrawal part of a large phase III trial.

Methods: Patients 2–19 yrs of age with active SJIA who had responded to open-label canakinumab treatment 4mg/kg/4wks sc, maintained a minimum adapted ACR Pediatric criteria [aACR] 30 for up to 32 weeks, and were steroid-free or had successfully reduced systemic steroids to a minimum dose, were randomized to either continue canakinumab or receive placebo until 37 flare events occurred. [1] Patients were considered to have completed the study if they entered clinical remission on medication (CRM), i.e. achieved 24 consecutive weeks of clinical inactive disease (CID). [2] A survival analysis of the time to worsening in aACR level, after randomization for the canakinumab and placebo groups was performed. Time to worsening is the time to fail to maintain at least the same level of aACR response seen at randomization. The change in the proportion in each group of those with CID was also evaluated.

Results: 100 pts were randomized to a canakinumab (n=50) or a placebo (n=50) group, of whom 26 (53%) and 27 (54%), respectively, had CID at the start of the randomization part. In the first 2 months, probability of maintaining aACR response was similar for both treatment groups. Thereafter, the probability of maintaining aACR response was greater in the canakinumab vs placebo groups. The median time to worsening in aACR level for patients in the placebo group was 141 days (95% CI: 85, 281), and could not be calculated for canakinumab as <50% of canakinumab group had a worsening in their aACR level by the end of this phase. The median duration of exposure