Cincinnati Children's

2015 Research Annual Report

Rheumatology

RESEARCH AND TRAINING DETAILS

Click to view members

Faculty	**10**
Joint Appointment Faculty	**2**
Research Students	**5**
Support Personnel	**16**
Direct Annual Grant Support	**$1,407,850**
Direct Annual Industry Support	**$839,732**
Peer Reviewed Publications	**27**

CLINICAL ACTIVITIES AND TRAINING

Clinical Staff	**1**
Clinical Fellows	**6**
Other Students	**63**
Inpatient Encounters	**615**
Outpatient Encounters	**5,594**

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Research Highlights

Excellence in Clinical Outcomes in Juvenile Arthritis

Improving outcomes of children living with juvenile idiopathic arthritis (JIA) is the mission of the international quality improvement collaborative Pediatric Rheumatology Care and Outcomes Improvement Network (PR-COIN). Esi Morgan DeWitt, MD, MSCE, is working with the learning networks core of the James M. Anderson Center for Health Systems Excellence, and has led PR-COIN to another year of growth. As principal investigator of several grants supporting this network of 17 pediatric rheumatology sites, the PR-COIN cohort consists of over 2,600 children with JIA. Data from patient visits are entered into a shared registry and used for clinical care, quality improvement and research. Network teams review data and share progress during monthly webinars. Parent volunteers are much involved in the PR-COIN improvement work, interacting closely with the rheumatology provider teams. Care providers from the Division of Rheumatology at Cincinnati Children's share best practices and advance quality improvement initiatives with the other PR-COIN teams during semiannual two-day learning sessions. The network has demonstrated success in improving JIA outcomes with an increasing proportion of children in the network reaching a state of clinical remission of JIA and also achieving better functional outcomes. Network sites have improved processes of medical care, including more reliable monitoring of medication safety, and increased counseling of patients on safe use of medications. PR-COIN has developed *JIA Medication Choice Cards* to facilitate shared decision making among providers, families and children with JIA. In the past year, PR-COIN introduced new informatics tools, which semi-automate the planning of patient visits and enhance population management; the network has received grant funding from AHRQ, PCORI and Pfizer.

Connecting the Silos: A Partnership to Improve Immunization Rates Among Adolescents with High-Risk Health Conditions

Jennifer Huggins, MD and Rebecca Brady, MD in the Division of Infectious Disease are co-principal investigators of a grant awarded by Pfizer. The funded research is aimed at improving the delivery and documentation of immunizations to adolescents with high-risk (chronic and immunocompromising) conditions. These high-risk teens often require additional vaccinations and/or schedule modifications to meet Advisory Committee on Immunization Practices (ACIP) guidelines. There are several barriers to proper delivery and documentation of immunizations to high-risk teens that this project hopes to address; there is a lack of knowledge by providers, as well as patients and parents, regarding vaccine recommendations, benefits and risks. With the exception of the influenza vaccine, there is no standard practice for administration of vaccines in most specialty clinics at Cincinnati Children's. Further, a central, accurate vaccination database accessible by the Primary Care Provider (PCP) and the specialists about vaccination status and administration is lacking. The ownership of the unique vaccination requirements for these patients who receive care from specialists in addition to their PCP is often unclear. The 2013 Infectious Diseases Society of America (IDSA) Clinical Practice Guideline for Vaccination of the Immunocompromised Host recommends that specialists share this responsibility with the PCP to ensure that appropriate vaccinations are administered to patients with high-risk health conditions. Since the start of this vaccination initiative, the team has implemented a reliable process to administer Prevnar 13 to immunocompromised adolescents in the Rheumatology Clinic, Inflammatory Bowel Disease (IBD) Center and the HIV clinics. As a result of this initiative, the percentage of immunocompromised adolescents vaccinated with PREVNAR13 increased from 20 to 80%. Given its success, this team effort will be expanded to additional vaccinations, and eventually to additional specialty clinics at Cincinnati Children's. Infections are a major cause of morbidity and mortality in our immunocompromised patients. Successful completion of this project will assure protection against preventable infections for our immunocompromised patients.

Functional genomics offers insights into macrophage activation syndrome in patients with Systemic JIA

Alexei Grom, MD, in collaboration with Kenneth Kaufman, PhD; John Harley, MD, PhD; and Kejian Zhang, PhD, used

functional genomics to explore the genetic causes of macrophage activation syndrome (MAS), a severe and often life-threatening complication of rheumatic diseases. These studies, published in *Arthritis and Rheumatology*, utilized family-based whole exome sequencing (WES) to identify shared genetic mutations of children who developed MAS. Dr. Grom found that patients with rheumatic disease who develop MAS often share genetic variants in genes that have been implicated in development of familial hemophagocytic lymphohistiocytosis, a group of rare genetic conditions that share many clinical features with MAS. Additionally, this research identified numerous new candidate genes that may contribute to MAS. Dr. Grom also authored two additional reports in *Nature Genetics* and *Arthritis Care Research* that identified genetic causes of recurrent MAS with other autoinflammatory syndromes. Together with Grant Schulert, MD, PhD, along with collaborators at Novimmune and two pediatric rheumatology centers in Italy, Alexei Grom completed a translational research study which suggests that interferon gamma is a key cytokine in the pathogenesis of MAS. Together, this year's research results paved the way for the first clinical trial in MAS, which is currently in its planning stage.

Research Flow Cytometry Core Provides Novel Technologies for Cincinnati Children's Investigators

Directed by Sherry Thornton, PhD, the Research Flow Cytometry Core (RFCC) is housed in the Division of Rheumatology, and provides state-of-the-art equipment to over 140 research investigators to perform single cell analysis. In the last year, funding from the Research Foundation enabled the Core to increase the capacity for highly multi-parametric flow cytometry that provides capability for more detailed cellular analysis. Furthermore, an educational program was developed for this technology and offered to our users. The Core is supported by three National Institutes of Health (NIH) grants (NIH AR473363, NIH DK78392 and NIH DK90971), the Cincinnati Rheumatic Disease Core Center, the Center for Excellence in Molecular Hematology and the Digestive Health Center. To enhance the research of Cincinnati Children's investigators, the RFCC works closely with other core facilities, for example: collaborations with Cincinnati Children's Gene Expression Core and the DNA Sequencing and Genotyping Core have improved the workflow of combining cell sorting and single cell analysis for RNA sequencing. Such innovative activities of the RFCC were presented at a workshop on Bridging Flow Cytometry with New Technologies at the 2015 annual meeting of the International Society for the Advancement of Cytometry in Glasgow, Scotland. The novel technique of examining RNA at the single cell level using flow cytometry has also been implemented into the RFCC.

Effective Ovarian Protection of Girls with Lupus Requiring Cyclophosphamide

Hermine Brunner MD, MSc, MBA, in collaboration with Susan Rose, MD, from the Division of Endocrinology, reported the results of a randomized, double-blind, placebo-controlled, dose-escalation study of the gondadotropin releasing hormone agonist (GnRH) triptorelin in girls requiring cyclophosphamide for severe life-threatening manifestations of lupus (NCT00124514). Published in *Arthritis & Rheumatology*, this international multi-center study was supported by a grant from the FDA Office of Orphan Product Development, Watson Pharmaceuticals and the Center for Clinical & Translational Science & Training. The goal of this clinical trial was to demonstrate the pharmacokinetics, safety and provisional efficacy of triptorelin when used for ovarian protection. The primary outcome was a weight-adjusted dose of triptorelin which provided complete ovarian suppression in at least 90% of the girls with lupus, as determined by GnRH stimulation testing. Secondary outcomes included the period of time required to achieve ovarian suppression and safety. The investigators reported that a weight-adjusted dose of triptorelin at 120 µg/kg body weight is needed to reach sustained complete ovarian suppression in at least 90% of the patients. After administration of the initial dose of triptorelin, 22 days were required to achieve complete ovarian suppression. The safety profile of triptorelin in the study population seemed acceptable, as rates of adverse events and serious adverse events per 100 patient months of follow-up were not higher in the triptorelin group as compared with the placebo group. Ovarian function was preserved in patients receiving triptorelin. The authors concluded that higher doses of triptorelin than those generally used for adult women are needed to achieve and maintain complete ovarian suppression in girls with lupus, but that high-dose triptorelin was safe and well tolerated. The study is among the first to provide guidance on evidence-based dosing of medications for children with lupus.

Pediatric Rheumatology Collaborative Study

The Pediatric Rheumatology Collaborative Study Group (PRCSG) is an international network of over 190 pediatric rheumatologists united in the design and performance a range of clinical studies to better define and gain FDA approval for new therapies for children with rheumatic and autoinflammatory diseases. For the last 25 years, the leadership and coordinating center for the PRCSG has been located in the Cincinnati Children's Division of Rheumatology.

In the past year, the PRCSG has been actively involved in the conduct of 16 clinical trials of new treatments for children with rheumatic diseases and six additional studies are in development. During the preceding year, the network published in the *Pediatric Rheumatology Online Journal* and in *Arthritis & Rheumatology* on the long term safety of an entire class of treatments, Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) and the relatively new biologic agent abatacept, respectively. Using a novel trial design developed here at Cincinnati Children's, the PRCSG in collaboration with Bin Huang, PhD, with the Division of Epidemiology & Biostatistics, and Dr. Phil Hashkes from the Jerusalem's Shaare Zedek Medical Center reported on the efficacy of the new biologic agent rilonacept when used in treatment of patients with poorly responsive familial mediterranean fever, the most common autoinflammatory disease in the world. As published in *Biomedical Research International*, rilonacept results in marked improvement of patient quality of life. Work continues on further defining the longer term effectiveness and safety of two new biologic treatments for systemic juvenile idiopathic arthritis (SJIA), the most severe and life-threatening form of JIA. Recent randomized placebo-controlled clinical trials performed by the PRCSG have demonstrated rapid and comprehensive improvement in over 80% of children with SJIA with either Interleukin-1 blockade (canakinumab) or Interleukin-6 blockade (tocilizumab). As a result of those trials, both agents have been approved by the FDA for the treatment of children with SJIA.

Significant Publications

Schulert GS, **Grom AA**. Pathogenesis of macrophage activation syndrome and potential for cytokine- directed therapies. *Annu Rev Med.* 2015;66:145-59.

> Macrophage activation syndrome, an acute episode of overwhelming inflammation caused by a cytokine storm is increasingly recognized as a life-threatening complication of systemic juvenile idiopathic arthritis. The nature of the predisposition for MAS in SJIA is still not well defined. The fact that MAS occurs in SJIA patients whose disease is controlled with new biologics blocking IL1 and IL-6, suggests that it has a component that is not dependent on underlying SJIA activity. Dr. Grom's research shows that component may be similar to that in infection-associated secondary hemophagocytic lymphohistiocytosis, i.e hypomorphic mutations affecting the cytolytic pathway. Whole exome/genome sequencing approaches to explore this further look promising.

Raghu H, Cruz C, Rewerts CL, Frederick MD, **Thornton S**, Mullins ES, Schoenecker JG, Degen JL, Flick MJ. Transglutaminase factor XIII promotes arthritis through mechanisms linked to inflammation and bone erosion. *Blood.* 2015;125(3):427-37.

> These studies demonstrate a role for the coagulation factor XIII (fXIII) in the pathogenesis of arthritis. Mice deficient in fXIIIA demonstrated reduced inflammatory arthritis and were partially protected from cartilage and bone destruction. This protection in part was mediated through mechanisms associated with reduced RANKL-mediated osteoclastogenesis. Therapeutics targeting fXIII activity may prove beneficial in limiting arthropathies and potentially other bone diseases.

Division Publications

1. Abulaban KM, Brunner HI. **Biomarkers for childhood-onset systemic lupus erythematosus**. *Curr Rheumatol Rep*. 2015; 17:471.

2. Beukelman T, Brunner H. **Trial Design, Measurement and Clinical Investigations**. In: JT Cassidy, RE Petty, RM Laxer, CB Lindsley, eds. *Textbook of Pediatric Rheumatology*. Philadelphia, PA: Elsevier Health Sciences; 2015:78-87.

3. Brunner H, Lomax KG, Levy S. **Half-life and safety of canakinumab in pediatric patients: comment on the article by Ilowite et Al**. *Arthritis Rheumatol*. 2015; 67:857-8.

4. Brunner HI, Klein-Gitelman MS, Zelko F, Beebe DW, Foell D, Lee J, Zaal A, Jones J, Roebuck-Spencer T, Ying J. **Blood-based candidate biomarkers of the presence of neuropsychiatric systemic lupus erythematosus in children**. *Lupus Sci Med*. 2014; 1:e000038.

5. Brunner HI, Ruperto N, Zuber Z, Keane C, Harari O, Kenwright A, Lu P, Cuttica R, Keltsev V, Xavier RM, Calvo I, Nikishina I, Rubio-Perez N, Alexeeva E, Chasnyk V, Horneff G, Opoka-Winiarska V, Quartier P, Silva CA, Silverman E, Spindler A, Baildam E, Gamir ML, Martin A, Rietschel C, Siri D, Smolewska E, Lovell D, Martini A, De Benedetti F, Paediatric Rheumatology International Trials Organisation P, Pediatric Rheumatology Collaborative Study G. **Efficacy and safety of tocilizumab in patients with polyarticular-course juvenile idiopathic arthritis: results from a phase 3, randomised, double-blind withdrawal trial**. *Ann Rheum Dis*. 2015; 74:1110-7.

6. Brunner HI, Silva CA, Reiff A, Higgins GC, Imundo L, Williams CB, Wallace CA, Aikawa NE, Nelson S, Klein-Gitelman MS, Rose SR. **Randomized, double-blind, dose-escalation trial of triptorelin for ovary protection in childhood-onset systemic lupus erythematosus**. *Arthritis Rheumatol*. 2015; 67:1377-85.

7. Canna SW, de Jesus AA, Gouni S, Brooks SR, Marrero B, Liu Y, DiMattia MA, Zaal KJ, Sanchez GA, Kim H, Chapelle D, Plass N, Huang Y, Villarino AV, Biancotto A, Fleisher TA, Duncan JA, O'Shea JJ, Benseler S, Grom A, Deng Z, Laxer RM, Goldbach-Mansky R. **An activating NLRC4 inflammasome mutation causes autoinflammation with recurrent macrophage activation syndrome**. *Nat Genet*. 2014; 46:1140-6.

8. De Benedetti F, Brunner H, Ruperto N, Schneider R, Xavier R, Allen R, Brown DE, Chaitow J, Pardeo M, Espada G, Gerloni V, Myones BL, Frane JW, Wang J, Lipman TH, Bharucha KN, Martini A, Lovell D, Paediatric Rheumatology International Trials O, the Pediatric Rheumatology Collaborative Study G. **Catch-up growth during tocilizumab therapy for systemic juvenile idiopathic arthritis: results from a phase III trial**. *Arthritis Rheumatol*. 2015; 67:840-8.

9. Feldon M, Sikora K, Huggins JL, Billings SD, McMasters R, Brunner HI. **Polyarticular arthritis and skin nodulosis in a 14 year old female**. *Arthritis Care Res (Hoboken)*. 2014; .

10. Grom AA. **Macrophage Activation Syndrome**. In: JT Cassidy, RE Petty, RM Laxer, CB Lindsley, eds. *Textbook of Pediatric Rheumatology*. Philadelphia, PA: Elsevier Health Sciences; 2014:642-649.

11. Grom AA. **Canakinumab for the treatment of systemic juvenile idiopathic arthritis**. *Expert Rev Clin Immunol*. 2014; 10:1427-35.

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13. Kaufman KM, Linghu B, Szustakowski JD, Husami A, Yang F, Zhang K, Filipovich AH, Fall N, Harley JB, Nirmala NR, Grom AA. **Whole-exome sequencing reveals overlap between macrophage activation syndrome in systemic**

juvenile idiopathic arthritis and familial hemophagocytic lymphohistiocytosis. *Arthritis Rheumatol*. 2014; 66:3486-95.

14. Lipstein EA, Dodds CM, Lovell DJ, Denson LA, Britto MT. **Making decisions about chronic disease treatment: a comparison of parents and their adolescent children**. *Health Expect*. 2014; .

15. Mina R, Klein-Gitelman MS, Nelson S, Eberhard BA, Higgins G, Singer NG, Onel K, Tucker L, O'Neil KM, Punaro M, Levy DM, Haines K, Ying J, Brunner HI. **Effects of obesity on health-related quality of life in juvenile-onset systemic lupus erythematosus**. *Lupus*. 2015; 24:191-7.

16. Minoia F, Davi S, Horne A, Demirkaya E, Bovis F, Li C, Lehmberg K, Weitzman S, Insalaco A, Wouters C, Shenoi S, Espada G, Ozen S, Anton J, Khubchandani R, Russo R, Pal P, Kasapcopur O, Miettunen P, Maritsi D, Merino R, Shakoory B, Alessio M, Chasnyk V, Sanner H, Gao YJ, Huasong Z, Kitoh T, Avcin T, Fischbach M, Frosch M, Grom A, Huber A, Jelusic M, Sawhney S, Uziel Y, Ruperto N, Martini A, Cron RQ, Ravelli A, Pediatric Rheumatology International Trials O, Childhood A, Rheumatology Research A, Pediatric Rheumatology Collaborative Study G, Histiocyte S. **Clinical features, treatment, and outcome of macrophage activation syndrome complicating systemic juvenile idiopathic arthritis: a multinational, multicenter study of 362 patients**. *Arthritis Rheumatol*. 2014; 66:3160-9.

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19. Ringold S, Hendrickson A, Abramson L, Beukelman T, Blier PR, Bohnsack J, Chalom EC, Gewanter HL, Gottlieb B, Hollister R, Hsu J, Hudgins A, Ilowite NT, Klein-Gitelman M, Lindsley C, Lopez Benitez JM, Lovell DJ, Mason T, Milojevic D, Moorthy LN, Nanda K, Onel K, Prahalad S, Rabinovich CE, Ray L, Rouster-Stevens K, Ruth N, Shishov M, Spalding S, Syed R, Stoll M, Vehe RK, Weiss JE, White AJ, Wallace CA, Sobel RE. **Novel method to collect medication adverse events in juvenile arthritis: results from the childhood arthritis and rheumatology research alliance enhanced drug safety surveillance project**. *Arthritis Care Res (Hoboken)*. 2015; 67:529-37.

20. Schulert GS, Grom AA. **Pathogenesis of macrophage activation syndrome and potential for cytokine- directed therapies**. *Annu Rev Med*. 2015; 66:145-59.

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22. Sil S, Thomas S, DiCesare C, Strotman D, Ting TV, Myer G, Kashikar-Zuck S. **Preliminary evidence of altered biomechanics in adolescents with juvenile fibromyalgia**. *Arthritis Care Res (Hoboken)*. 2015; 67:102-11.

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27. Zhang M, Behrens EM, Atkinson TP, Shakoory B, Grom AA, Cron RQ. **Genetic defects in cytolysis in macrophage activation syndrome**. *Curr Rheumatol Rep*. 2014; 16:439.

Faculty, Staff, and Trainees

Faculty Members

Hermine Brunner, MD, MSc, MBA, Professor
Leadership Division Director

Edward H. Giannini, MSc, DrPH, Adjunct
Leadership Professor Emeritus

Alexei A. Grom, MD, Professor
Leadership Research Director

Michael Henrickson, MD, MPH, Associate Professor
Leadership Telemedicine Program Director

Jennifer Huggins, MD, Associate Professor
Leadership Fellowship and Education Program Director

Daniel Joe Lovell, MD, MPH, Professor
Leadership Joseph E. Levinson Endowed Chair in Pediatric Rheumatology; Associate Division Director; Clinic Co-Director

Rina Mina, MD, Assistant Professor
Leadership Quality Improvement Co-Leader & Transitional Service Co-Leader

Esi Morgan DeWitt, MD, MSCE, Associate Professor
Leadership Quality Improvement Operations Director

Sherry Thornton, PhD, Assistant Professor
Leadership Director of the Flow Cytometry Core; SURF Director

Tracy Ting, MD, Assistant Professor
Leadership Clinic Co-Director

Joint Appointment Faculty Members

Halima Moncrieffe, PhD, Instructor (Center for Autoimmune Genomics and Etiology)

Susan Thompson, PhD, Professor (Center for Autoimmune Genomics and Etiology)

Clinical Staff Members

- **Janalee Taylor, MSN, RN, CNS, CNP**, Quality Improvement Co-Leader & Transition Service Co-Leader

Trainees

- **Khalid Abulaban, MD**, PGY7, Penn State Hershey Medical Center
- **Michal Feldon, MD**, PGY5, Tel-Aviv University
- **Michael Holland, MD**, PGY5, Stanford University
- **Jordan Jones, DO**, PGY6, University of Kansas
- **Grant Schulert, MD**, PGY6, Children's Hospital at Vanderbilt
- **Jessica Turnier, MD**, PGY4, University of Colorado

Grants, Contracts, and Industry Agreements

Grant and Contract Awards		Annual Direct

Brunner, H

Optimization of Outcome Measures For Clinical Trials in Children with Lupus

National Institutes of Health

U01 AR067166	9/15/2014-9/14/2017	$145,167

Cincinnati Center for Innovative Medicine in Adult & Pediatric Rheumatology

National Institutes of Health

UH2 AR067692	9/26/2014-9/30/2015	$160,256

Critical Translational Studies in Pediatric Nephrology - Lupus Nephritis Core

National Institutes of Health

P50DK096418	9/21/2012-8/31/2017	$110,144

Brunner, H / Bennett, M

Innovative Efficacy Measures of Lupus Nephritis Therapies

National Institutes of Health

U01 AR065098	7/26/2013-6/30/2016	$148,962

Grom, A

MUNC13-4 Gene Polymorphisms in Macrophage Activation Syndrome and Systemic Juvenile Idiopathic Arthritis

National Institutes of Health

R01 AR059049	8/8/2011-7/31/2016	$220,500

Gene Expression in Pediatric Arthritis - Project 4

National Institutes of Health

P01AR048929	9/1/2002-8/31/2016	$86,128

Huggins, J

Pediatric Rheumatology Fellowship Program

Abbott Laboratories

	7/1/2014-6/30/2015	$40,000

2014-2015 Amgen Fellowship Training Award

Rheumatology Research Foundation

	7/1/2014-6/30/2015	$25,000

Lovell, D

Gene Expression in Pediatric Arthritis - Project 2

National Institutes of Health

P01 AR048929	9/1/2002-8/31/2016	$37,827

Morgan DeWitt, E

PR-COIN Quality Improvement Collaborative - Medical Education

Pfizer, Inc.

	9/15/2014-9/14/2015	$234,375

Schulert, G

Omics of Lung Diseases

National Institutes of Health

K12 HL119986	9/1/2013-5/31/2018	$105,250

Thornton, S

Cincinnati Rheumatic Disease Core Center - Flow Core

National Institutes of Health

P30 AR047363	3/15/2001-6/30/2016	$56,567

Digestive Health Center: Bench to Bedside Research in Pediatric Digestive Disease - Flow Cytometry Core

National Institutes of Health

P30 DK078392	7/1/2007-5/31/2017	$37,674

	Current Year Direct	**$1,407,850**

Industry Contracts

Brunner, H

Abbott Laboratories	$9,355
Roche Laboratories, Inc	$166,402
Eli Lilly and Company	$7,961
GlaxoSmithKline	$375
Pfizer Inc.	$11,900
UCB Pharma, Inc	$46,138

Huggins, J

Genentech, Inc.	$1,500

Lovell, D

Astrazeneca	$2,166
Bristol -Myers Squibb	$438,283
Genentech, Inc.	$50,464
Novartis Pharmaceuticals	$54,854
Roche Laboratories, Inc	$50,334

Current Year Direct Receipts	**$839,732**
Total	**$2,247,582**

Tocilizumab Shown to be Safe and Effective as Novel Treatment for Children With Juvenile Idiopathic Arthritis

Hermine Brunner, MD, MSc, MB

RESEARCH AND TRAINING DETAILS

Faculty	10
Joint Appointment Faculty	2
Research Students	5
Support Personnel	16
Direct Annual Grant Support	$1.4M
Direct Annual Industry Support	$839,732
Peer Reviewed Publications	27

Brunner HI, Ruperto N, Zuber Z, Keane C, Harari O, Kenwright A, Lu P, Cuttica R, Keltsev V, Xavier RM, Calvo I, Nikishina I, Rubio-Perez N, Alexeeva E, Chasnyk V, Horneff G, Opoka-Winiarska V, Quartier P, Silva CA, Silverman E, Spindler A, Baildam E, Gamir ML, Martin A, Rietschel C, Siri D, Smolewska E, Lovell D, Martini A, De Benedetti F, Paediatric Rheumatology International Trials Organisation P, Pediatric Rheumatology Collaborative Study G. Efficacy and safety of tocilizumab in patients with polyarticular-course juvenile idiopathic arthritis: results from a phase 3, randomised, double-blind withdrawal trial. *Ann Rheum Dis*. 2015;74(6):1110-1117.

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Annals of Rheumatic Diseases

Children with polyarticular juvenile idiopathic arthritis (JIA) can now be treated safely and effectively with tocilizumab, an interleukin-6 receptor inhibitor drug, according to a 58-center global study coordinated and co-designed at Cincinnati Children's.

An extended report on the results of the Phase III CHERISH study was first published online May 16, 2014, in the *Annals of the Rheumatic Diseases*. The U.S. Food and Drug Administration (FDA) has used positive results of this clinical trial to expand the indication for tocilizumab, which had previously been approved to treat moderate to severe active rheumatoid arthritis and systemic JIA.

Tocilizumab is the first new treatment for polyarticular JIA in five years, and significantly enhances options for treating joint pain and swelling in children with JIA.

Hermine Brunner, MD, MSc, MB, Director of the Division of Rheumatology at Cincinnati Children's and Scientific Director of the multinational Pediatric Rheumatology Collaborative Study Group (PRCSG), led the study. Daniel Lovell, MD, MPH, Chairman of the PRCSG and Clinical Director of Rheumatology, also participated in study design and coordination.

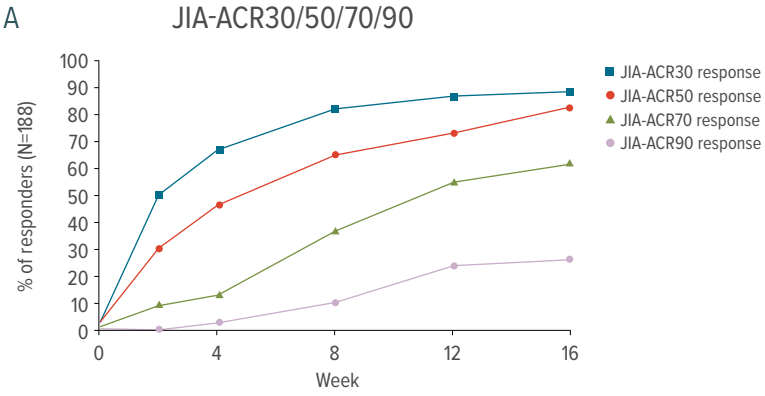
The CHERISH study showed that 89 percent of children treated with tocilizumab markedly improved within 16 weeks, including significantly fewer JIA exacerbations or flares.

The study enrolled 188 patients with active polyarticular JIA, ages 2-17 years. All received monthly infusions of tocilizumab for 16 weeks. Those whose symptoms improved then joined a 24-week, double-blind phase in which half the patients received a placebo and half continued on the drug.

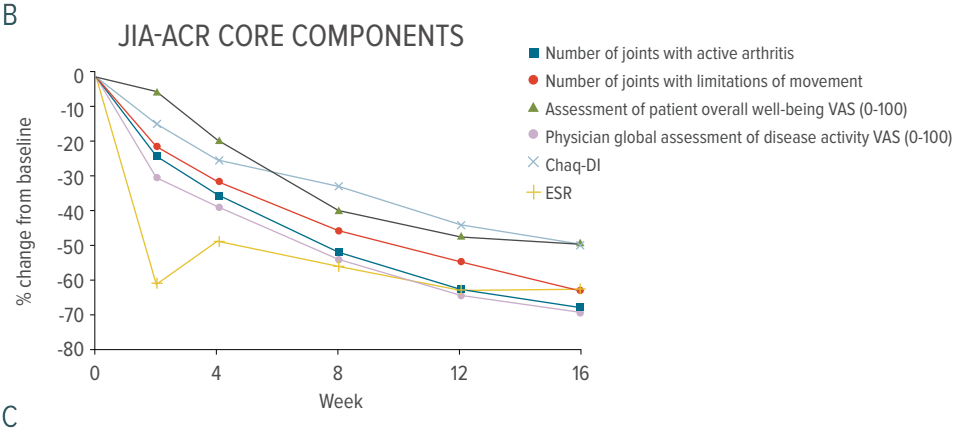
Arthritis symptoms flared in 48 percent of placebo patients versus 26 percent in the tocilizumab group. Side effects, primarily upper respiratory infections, occurred in 8.5 percent of participants.

"The overall pediatric safety profile of tocilizumab was consistent with that seen in adults with rheumatoid arthritis," Brunner says. "Most importantly, tocilizumab provides sustained and clinically meaningful improvement of polyarticular JIA."

A



B



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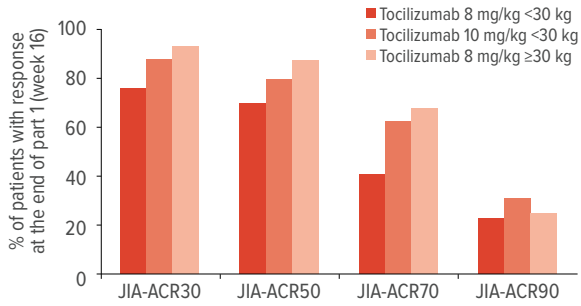
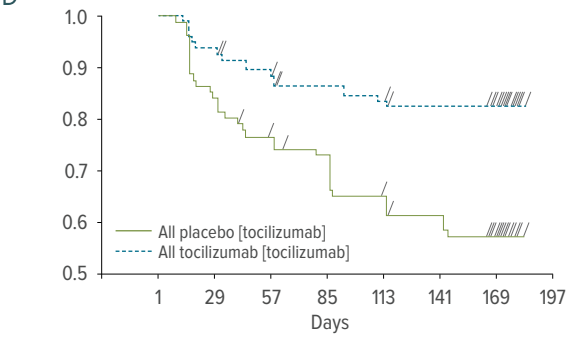


D



All placebo [tocilizumab] (n)	81	66	58	51	45	43	11	0
All tocilizumab [tocilizumab] (n)	82	75	67	66	61	61	28	0

These four charts, published in the *Annals of Rheumatic Diseases,* show: (A) Improvement of JIA as measured by the American College of Rheumatology Criteria for improvement at JIA-ACR30/50/70/90 levels after open-label treatment with tocilizumab for 16 weeks; (B) Improvements in the individual components contributing to the measurement of JIA-ACR level response of children with polyarticular JIA treated with tocilizumab; (C) Treatment responses considering dosing regimens suggested by pre-trial pharmacokinetic modeling; and (D) Time to JIA-ACR30 flare during the double-blinded phase of the trial when patients with at least a JIA ACR30 response by week 16 were randomized to continue tocilizumab or newly receive placebo.