BPCA Rheumatology Therapeutic Area Working Group

Working group co-chairs:

Mara L Becker, MD, MSCE
Associate Professor of Pediatrics
Children's Mercy Hospitals and Clinics

Laura Schanberg, MD
Professor of Pediatrics
Duke University Medical Center

DEPARTMENT OF HEALTH & HUMAN SERVICES · USA
NATIONAL INSTITUTES OF HEALTH
Eunice Kennedy Shriver NICHD
National Institute of Child Health & Human Development

History of the subspecialty

- **Do children really get arthritis??**
  - Reports of arthritis in children over 100 yrs ago
  - National professional organizations did not recognize pediatric rheumatology until mid-1970's
    - » 1976: ARA "Park City meeting" no more than 30 pediatric rheumatologists in the US at the time
    - » Pediatric Rheumatology Collaborative Study Group (PRCSG) developed standard methodology for the design, conduct, and analysis of drug trials in children with rheumatic disease

Barriers to therapeutic development

- **Diseases are rare**
- **Small workforce→ large clinical need, research naive**
- **Unknown pathophysiology and etiology**
- **Heterogeneous phenotype**
- **Lack of validated outcome measures**
- **Barriers inherent to pediatric studies**
  - vulnerable population
  - few biomarkers
  - ethics/acceptability of placebo
  - paternalism

DEPARTMENT OF HEALTH & HUMAN SERVICES USA
NATIONAL INSTITUTES OF HEALTH
Eunice Kennedy Shriver NICHD
National Institute of Child Health & Human Development

Overcoming barriers: collaborative efforts

- **PRCSG**
  - Industry-sponsored studies
  - Collaboration with PRINTO (Paediatric Rheumatology InterNational Trials Organization)
- **Childhood Arthritis and Rheumatology Research Alliance (CARRA)**
  - North American investigator-initiated network focused on facilitating high quality collaborative clinical and translational research
  - CARRA Registry
    - » Consensus Treatment Plans (CER)
    - » CARRA CoRe

CARRA registry enrollment

Disease	Count
JIA	5669
SLE	825
JDM	540
Localized scleroderma	301
Vasculitis	162
JPFS	153
MCTD	138
Idiopathic Uveitis	62
Systemic sclerosis	48
Auto-inflammatory disease	45
Sarcoid	44
Primary Sjogrens	14
TOTAL Disease Count	8001
TOTAL Enrollment in InForm	8131

Number of Follow Up Visits 11/26/2012	
1 Follow-Up	4,472
2 Follow-Ups	2,028
3 Follow-Ups	730
4 Follow-Ups	167
5 Follow-Ups	22
6 Follow-Ups	12
7 Follow-Ups TOTAL	5
Follow-Ups	7,436

NATIONAL INSTITUTES OF HEALTH

Eunice Kennedy Shriver NICHD National Institute of Child Health & Human Development

First pediatric rheumatology WG meeting

- **Several themes:**
  - "Older" drugs commonly used with scant pediatric data to guide use
  - Formulation remains a major issue
  - Newer biologics lack indications for common usages

Disease focus for rheum WG subcommittees

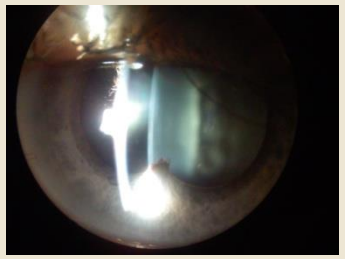
- **Idiopathic Uveitis**
  - *Andreas Reiff MD, Steven Spalding MD, Mary Toth MD*
- **Juvenile Idiopathic Arthritis**
  - *Polly Ferguson MD (Chair), Marcia Buck PharmD, William Rodriguez MD PhD, Carol Wallace MD, Pamela Weiss MD*
- **Bone biology**
  - *Gordon Klein MD, Mary Toth MD*
- **Pediatric Systemic Lupus Erythematosus**
  - *Larry Jung MD (Chair), Rond Portman MD, Marilynn Punaro MD, Scott Weir PharmD PhD*
- **Juvenile Fibromyalgia**
  - *Michael Reed PharmD (Chair), Douglas Silverstein MD, Janice Sullivan MD, Surendra Varma MD*

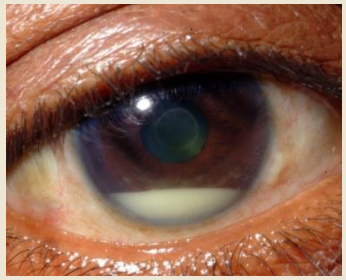
NICHD National Institute of Child Health & Human Development

IDIOPATHIC INFLAMMATORY UVEITIS

DEPARTMENT OF HEALTH & HUMAN SERVICES USA
NATIONAL INSTITUTES OF HEALTH
Eunice Kennedy Shriver NICHD
National Institute of Child Health & Human Development

Idiopathic non-infectious uveitis: background





- **Inflammation of the uvea of the eye**
  - Anterior, intermediate, posterior, pan
- **10-15% of blindness in US caused by uveitis and leading cause of acquired blindness in childhood[1]**
- **JIA most frequent cause of chronic intra-ocular inflammation in children**
  - Present in 10-20% of kids with JIA

Uveitis: clinical need

- **Only FDA approved treatments for adult and pediatric non-infectious uveitis are topical, oral, or intravitreal steroids**
- **Role of immunosuppressive drugs in refractory or steroid dependent uveitis is poorly studied**
- **Current treatment options based on expert opinion, open label studies and anecdotal case series**

Heiligenhaus, A., Michels, H., Schumacher, C., Kopp, I., Neudorf, U., Niehues, T… Zierhut, M. (2011). Evidence Based,Interdisciplinary Guidelines for Anti-Inflammatory Treatment of Uveitis Associated with Juvenile Idiopathic Arthritis. *Rheumatology International* , *32(5),* 1121-1133.

Simonini, G., Cantarini, L., Bresci, C., Lorusso, M., Galeazzi, M., & Cimaz, R. (2010). Current Therapeutic Approaches to Autoimmune Chronic Uveitis in Children. *Autoimmunity Rev, 9,* 674-683

Uveitis: knowledge gaps - methotrexate

- **Most commonly used DMARD**
  - Safety and adverse effects well-studied in pediatric populations
    - » **Infections, cytopenias, GI upset, hepatic toxicity**
- **Effective in adults > children?**
- **Approved for pJIA at low doses (10mg/m^2)**
  - Higher doses and SC route used for uveitis
    - » **Optimal dose or route for treatment of uveitis not known**

1. Simonini G, et al. *Rheumatology* (2012)

Goebel, J.C., Roesel, H., Heinz, C., Michels, H., Ganser, G., & Heiligenhaus, A. (2011). Azathioprine as a Treatment Option for Uveitis in Patients with Juvenile Idiopathic Arthritis. *Br J Ophthalmol, 95,* 209-213. Goebel JC, et al. *Br J Ophthalmol* (2011) 95:209-213.

Chang, P.Y., Giuliari, G.P., Shaikh, M., Thakuria, P., Makhoul, D., & Foster, C.S. (2011). Mycophenolate Mofetil Monotherapy in the Management of Paediatric Uveitis. *Eye*, *25,* 427-435.

NATIONAL INSTITUTES OF HEALTH
Eunice Kennedy Shriver NICHD
National Institute of Child Health & Human Development

Uveitis: knowledge gaps – biologics

- **Cytokine blocking agents used in MTX resistant patients**
- **Utility/indication for biologic use for treatment of uveitis? Appropriate dosing? Long term safety?**

Recommendations - MTX

- **1) indication and 2) dosing guidelines**
  - Pts with chronic uveitis who fail minimum of 4 week trial of topical, subtenon, intravitreal or oral steroids
  - Begin with MTX doses of 10-15mg/m^2 SC, titrate dose up to 1mg/kg/week (max 40mg weekly)
  - Outcomes at 6 months: anterior chamber cell density, intraocular pressure, flare, visual acuity, ability to taper steroids

Recommendations – biologics (MTX failure)

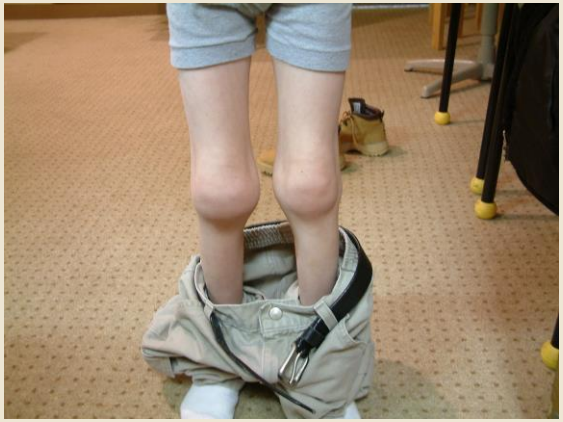
- **1) indication, 2) dosing guidelines, 3) long term safety, and 4) when to withdraw**
  - Anti-TNF-α:
    - » Vast variability of use in clinical practice. Infliximab dosed q 4 weeks at doses 5-20mg/kg/dose to treat severe uveitis
  - CTLA-4 blockers (abatacept)
    - » Anecdotal reports of efficacy in refractory patients
  - Anti-IL-6 (tocilizimab)
  - Anti-IL-1 (anakinra, canakinumab)
  - Outcome measures: same as mtx studies
  - Long term safety/efficacy studies use CARRA Registry
  - When to withdraw therapy?

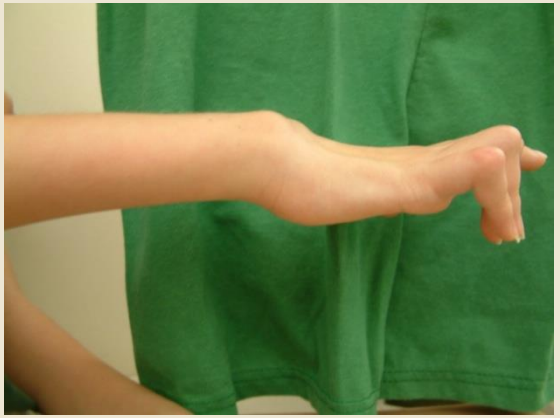
JUVENILE IDIOPATHIC ARTHRITIS

DEPARTMENT OF HEALTH & HUMAN SERVICES USA
NATIONAL INSTITUTES OF HEALTH
Eunice Kennedy Shriver NICHD
National Institute of Child Health & Human Development

JIA: background

- Immunoinflammatory disorder of unknown etiology
- Affects approximately 300,000 children in US alone
- Heterogeneous presentation





JIA: background

- **2011 ACR recommendations for treatment of JIA**
  - Scant strong evidence, utilized available descriptive studies and expert consensus
- **Consensus treatment plans for CER are being developed and piloted utilizing the CARRA registry**

Beukelman, T., Patkar, N.M., Saag, K.G., Tolleson-Rinehart, S., Cron, R.Q., DeWitt, E.M…Ruperto, N. (2011). American College of Rheumatology Recommendations for the Treatment of Juvenile Idiopathic Arthritis: Initiation and Safety Monitoring of Therapeutic Agents for the Treatment of Arthritis and Systemic Features. *Arthritis Care Res, 63,* 465-482.

DeWitt, E.M., Kimura, Y., Beukelman, T., Nigrovic, P.A., Onel, K., Prahalad, S…Wallace, C.A. (2012). Juvenile Idiopathic Arthritis Disease-Specific Research Committee of Childhood Arthritis Rheumatology and Research Alliance. (2012). *Arthritis Care Res,* 64(7)*, 1001-1010.*

JIA: clinical need

- **Several recommended therapies for JIA do not currently have an indication for use**
  - anti-IL-1 therapy and infliximab
- **Long term large scale safety studies needed to detect rare adverse events**

JIA: knowledge gaps

- ***Anakinra (anti-IL-1) in sJIA***
  - Optimal dosing UNKNOWN, NO pediatric PK data
  - Formulation issues
    - » Painful
    - » Difficult to titrate for weight based dosing (100mg/0.67ml vials)
      - » Requires transfer of drug from original pre-filled syringes to accommodate for smaller doses
  - Targeted sJIA patient populations
    - » Subset of pts NOT responsive or lose response over time- how can we identify these patients?

Nigrovic, P.A., Mannion, M., Prince, F.H., Zeft, A., Rabinovich, C.E., van Rossum, M.A…Higgins, G.C. (2011). Anakinra as First-Line Disease-Modifying Therapy in Systemic Juvenile Idiopathic Arthritis: Report of Forty-Six Patients from an International Multicenter Series. *Arthritis Rheum, 63,* 545-555.

Kineret Prescribing Information. Amgen. (2003). Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2003/anakamg062703LB.pdf. Accessed October 3, 2012.

Zeft, A., Hollister, R., LaFleur, B., Sampath, P., Soep, J., McNally, B., & Bohnsack, J. (2009). Anakinra for Systemic Juvenile Arthritis: the Rocky Mountain Experience. *J Clin Rheumatol*,15, 161–164.

Gattorno, M., Piccini, A., Lasiglie, D., Tassi, S., Brisca, G., Carta, S…Rubartelli, A. (2008).The Pattern of Response to Anti–Interleukin-1 Treatment Distinguishes Two Subsets of Patients with Systemic-Onset Juvenile Idiopathic Arthritis. *Arthritis Rheum*, *58,* 1505–1515.

Lequerre T, et al. *Ann Rheum Dis* (2008) 67:302-8.

JIA: knowledge gaps

- ***Infliximab (anti-TNF-α)***
  - Poorly designed RCT prevented an indication for JIA, but case reports, case series and open label clinical trials report efficacy
  - ***It is commonly used off label***
    - » Optimal dosing? Differences in weight normalized clearance and volume in kids less than 7 yrs -- due to differences in REE?
    - » Optimal timing? Early vs. step up approach?
    - » Variability in response (up to 40% do not respond or lose response over time)? Antibodies to drug?
    - » Long term safety

Virkki, L M., Valleala, H., Takakurbo, Y., Vuotila, J., Relas, H., Komulainen, R Nordstrom, D.C. (2011). Outcomes of Switching Anti-TNF Drugs in Rheumatoid Arthritis--a Study Based on Observational Data from the Finnish Register of Biological Treatment (ROB-FIN). *Clin Rheumatol,* 30, 1447-1454.

Gerlone, V., Pontikaki, I., Gattinara, M., Desiati, F., Lupi, E., Lurati, A Fantini, F. (2005). Efficacy of Repeated Intravenous Infusions of an Anti-Tumor Necrosis Factor Alpha Monoclonal Antibody, Infliximab, in Persistently Active, Refractory Juvenile Idiopathic Arthritis: Results of an Open-Label Prospective Study. *Arthritis Rheum, 52,* 548-553.

Tynjala, P., Vahasalo, P., Tarkiainen, M., Kroger, L., Aalto, K., Malin, M Lahdenne, P. (2011). Aggressive Combination Drug Therapy in Very Early Polyarticular Juvenile Idiopathic Arthritis (ACUTE-JIA): a Multicentre Randomised Open-Label Clinical Trial. *Ann Rheum Dis, 70,*1605-1612.

Lahdenne, P., Vahasalo, P. & Honkanen, V. (2003). Infliximab or Etanercept in the Treatment of Children with Refractory Juvenile Idiopathic Arthritis: an Open Label Study. *Ann Rheum Dis*, *62,* 245–247.

Ruperto, N., Lovell, D J., Cuttica, R., Woo, P., Mejorin, S., Wouters, C Giannini, E.H. (2010). Long-Term Efficacy and Safety of Infliximab plus methotrexate for the treatment of polyarticular-Course Juvenile Rheumatoid Arthritis: Findings from an Open-Label Treatment Extension. *Ann Rheum Dis, 69,* 718-722.

Goldman., J., Davis, H.Z., & Kearns, H.G. (2012). *Infliximab Clearance in Children: Potential Association with Resting Energy Expenditure. Ann Paediatr Rheum, 1,* 120-125.

NATIONAL INSTITUTES OF HEALTH

Eunice Kennedy Shriver NICHD National Institute of Child Health & Human Development

JIA: knowledge gaps

- **Long term large scale safety studies important to understand risk vs. benefits**
  - Traditional single product Phase IV registries inadequate to determine long term safety
    - » Detection of rare adverse events requires 10,000 + pt years of follow up
    - » Numbers of JIA pts available for participation is limited- all competing to recruit from same pool
    - » Most kids on multiple agents serially over time, making it difficult to prove causality
    - » Need to consider the contribution of the underlying disease as well--need registry with large numbers of patients with varied medication exposures

NATIONAL INSTITUTES OF HEALTH
Eunice Kennedy Shriver NICHD
National Institute of Child Health & Human Development

JIA: recommendations - biologics

- **Anakinra:**
  - PK studies in children
  - Efficacy studies in sJIA
  - Collaborate with manufacturer on development of a pediatric friendly formulation or safer method of titrating dose
  - Targeted biomarker studies to determine which sJIA subjects will respond to anti IL-1 vs anti IL-6 therapy
  - Long term safety studies
    - » CARRA Registry
    - » CARRA CoRe

JIA: recommendations - biologics

- **Infliximab**
  - Developmentally targeted PK studies to determine if higher doses required in younger children (e.g. tocilizumab)
  - Studies to investigate variability in response to individualized therapeutic decisions, i.e. biomarkers, pharmacogenomic studies, HACAs
  - Long term safety studies
    - » CARRA registry
    - » CARRA CoRe

JIA: recommendations - safety

- **Long term large scale safety studies**
  - Formal support for CARRA-Consolidated Registry (CoRe), a novel pharmcosurveillance model based on established multicenter CARRA registry.

BONE BIOLOGY

NATIONAL INSTITUTES OF HEALTH
Eunice Kennedy Shriver NICHD
National Institute of Child Health & Human Development

Bone biology: background

- **Bone metabolism of concern due to risk factors for osteopenia/osteoporosis:**
  - Long term steroid use to treat underlying diseases
  - Disordered inflammatory cytokines
- **Bone loss in childhood increases risks of morbidity in adulthood**

Bone biology: background

- **Bisphosphonates are FDA approved for treatment or prevention of glucocorticoid induced osteoporosis:**
  - Alendronate
  - Risendronate
  - Zoledronic acid
- **However, no drugs approved for this indication in children**

Bone biology: clinical need

- **Children with rheumatic disease (SLE, JIA, JDM) have decreased bone mineral density and potentially lowered peak bone mass**
  - Peak bone mass attained during adolescence is critical in determining adult fracture risk
- **Challenges diagnosing osteopenia/osteoporosis in children**
  - Pediatric-based references for DXA
  - Role of quantitative computed tomography (QCT)
  - Role of US

Rouster-Stevens, K.A., & Klein-Gitelman, M.S. (2005). Bone Health in Pediatric Rheumatic Disease. *Curr Opin Pediatr, 17,* 703-708.

Bone biology: knowledge gaps

- **Bone density assessment**
  - Misinterpretation due to adult norms
  - What modality to use for assessment?
    - » DXA still gold standard, but what is role of US and QCT?
  - Frequency of monitoring for safety/cost effectiveness?

Gafni, R.I., & Baron J (2004). Overdiagnosis of Osteoporosis in Children Due to Misinterpretation of Dual Energy X-Ray Absorptiometry (DEXA). *J Pediatr*, *144,* 253-257.

Hartman, C., Shamir, R., Eshach-Adiv, O., Iosilevsky, G., & Brik, R. (2004). Assessment of Osteoporosis by Quantitative Ultrasound versus Dual Energy X-Ray Absorptiometry in Children With Chronic Rheumatic Diseases. *J Rheumatol*, *31,* 981-985.

Prevrhal, S., Fuerst, T., Fan, B., Njeh, C., Hans, D., Uffmann, M…Genant, H.K. (2001). Quantitative Ultrasound of the Tibia Depends on Both Cortical Density and Thickness. *Osteoporos Int*, *12,* 28-34.

Bukhari, M. (2009). The National Osteoporosis Guideline Group's New Guidelines: What is New? *Rheumatology, 48,* 327-329.

Engelke, K., Libanati, C., Liu, Y., Wang, H., Austin, M., Fuerst, T…Genant, H.K. (2009). Quantitative Computed Tomography (QCT) of the Forearm Using General Purpose Spiral Whole-Body CT Scanners: Accuracy, Precision and Comparison with Dual-Energy X-Ray Absorptiometry (DXA). *Bone, 45,*110-118.

Trimpou P, et al: *Eur J Radiol* (2009)

Bone biology: knowledge gaps

- **Treatment for osteoporosis**
  - Evidence suggests long term safety and efficacy of bisphosphonates in children
    - » Pediatric PK studies of zoledronic acid and OI (FDA website)
    - » Studies specific to steroid use in children with rheumatic disease showed sustained increase in BMD and well tolerated
  - Binding to bone and prolonged renal excretion (7 yrs) raises long term safety concerns

Ward, L., Tricco, A.C., Phoung, P., Cranney, A., Barrowman, N., Gaboury, I…Moher, D. (2007). Bisphosphonate Therapy for Children and Adolescents with Secondary Osteoporosis. *Cochrane Database Syst Rev*, *4,* CD005324.

Bachrach, L.K., & Ward, L.M. (2009). Clinical Review 1: Bisphosphonate Use in Childhood Osteoporosis. *J Clin Endocrinol Metab, 94,* 400-409.

Inoue, Y., Shimojo, N., Suzuki, S., Arima, T., Tomiita, M., Minagawa, M., & Kohno, Y. (2008). Efficacy of Intravenous Alendronate for the Treatment of Glucocorticoid-Induced Osteoporosis in Children with Autoimmune Diseases. *Clin Rheumato, 27,* 909-912.

Bianchi, M.L., Cimaz, R., Bardare, M., Zulian, F., Lepore, L, Boncompagni, A…Falcini, F. (2000). Efficacy and Safety of Alendronate for the Treatment of Osteoporosis in Diffuse Connective Tissue Diseases in Children: A Prospective Multicenter Study. *Arthritis Rheum, 43,* 1960-1966.

Cimaz, R., Gattorno, M., Sormani, M.P., Falcini, F., Zulian, F., Lepore, L…Bianchi, M.L. (2002). Changes in Markers of Bone Turnover and Inflammatory Variables during Alendronate Therapy in Pediatric Patients with Rheumatic Diseases. *J Rheumatol, 29,* 1786-1792.

Rudge, S., Hailwood, S., Horne, A., Lucas, J., Wu, F., & Cundy, T. (2005). Effects of Once-Weekly Oral Alendronate on Bone in Children on Glucocorticoid Treatment. *Rheumatology, 44,* 813-818.

Papapoulos, S.E., & Cremers, S.C. (2007). Prolonged Bisphosphonate Release after Treatment in Children. *N Engl J Med*, *356,* 1075-1076.

Bone biology: knowledge gaps

- **Prevention of osteoporosis**
  - Role of bisphosphonates in conjunction with glucocorticoids
  - More aggressive use of steroid sparing agents
    - » Impact of disease activity vs. glucocorticoids on BMD

Bone biology: recommendations

- **RCT administering a single dose of bisphosphonate in patients started on long term steroids with DXA monitoring at 3,9,15 and 24 months**
  - Incorporate QCT, US in addition to DXA
    - » Effect of bisphosphonates on bone loss
    - » Safety
    - » Appropriate frequency of BMD monitoring
    - » Compare imaging modalities

PEDIATRIC SYSTEMIC LUPUS ERYTHEMATOSUS

DEPARTMENT OF HEALTH & HUMAN SERVICES USA
NATIONAL INSTITUTES OF HEALTH
Eunice Kennedy Shriver NICHD
National Institute of Child Health & Human Development

pSLE: background

- **15-20% of all SLE starts in childhood**
- **Worse in children**
  - higher disease severity
  - more organ involvement, especially renal
  - longer burden of disease
  - noncompliance
- **Immune system not mature**
- **Stronger genetic component**
- **Growth and body image issues**

pSLE: background

- **Wide variability in treatment**
- **CARRA consensus treatment plan for nephritis induction therapy**
  - Pilot comparing standard NIH protocol with cyclophosphamide vs mycophenolate with three different steroid regimens is underway
- **High rate of complications, short and long term, with current therapies**
  - Corticosteroids
  - Cyclophosphamide

Mina, R., Scheven, E., Ardoin, S.P., Eberhard, B.A., Punaro, M., Iiowite, N…Brunner, H.I. (2012). Consensus Treatment Plans for Induction Therapy of Newly Diagnosed Proliferative Lupus Nephritis in Juvenile Systemic Lupus Erythematosus. *Arthritis Care Res, 64,* 375–383.

pSLE: clinical need

- **No clinical trials in primary pSLE treatment**
- **No drugs specifically indicated for pSLE**
- **No outcome measures designed specifically for pSLE**
- **Reduce lifetime exposure to corticosteroids and cyclophosphamide**

DEPARTMENT OF HEALTH & HUMAN SERVICES USA
NATIONAL INSTITUTES OF HEALTH
Eunice Kennedy Shriver NICHD
National Institute of Child Health & Human Development

pSLE: knowledge gaps

- Lowest effective cyclophosphamide dose
- Treatment of refractory pSLE
- Treatment of extra-renal lupus, particularly neuropsychiatric lupus
- Pediatric dose, effectiveness, and safety of hydroxychloroquine

pSLE: recommendations - cyclophosphamide

- **Clinical trial comparing efficacy of Euro Lupus protocol (low dose) vs. NIH protocol (high dose) for pediatric proliferative nephritis induction.**
  - Provide efficacy and safety data not currently available for the most commonly used regimen in children.
  - Need to establish pediatric dosing Euro-lupus protocol

pSLE: recommendations - corticosteroids

- **Clinical trial comparing the safety and efficacy of IV methylprednisolone with cyclophosphamide, mycophenolate, and rituximab in pSLE-induced seizures and cerebral vascular events**
  - Utlize interferon signature, other biomarkers as well as standard clinical outcome measures
- **Support for CARRA CTPs comparing corticosteroid dosing regimens**

pSLE: recommendations - hydroxychloroquine

- **Used off label for several pediatric rheumatic diseases**
  - pSLE, primary Sjogren's, drug-induced SLE, JDM, JIA
- **Use CARRA Registry to study safety**
  - Add on PK studies to develop age-appropriate dosing
- **Develop a liquid formulation and/or smaller tablets to facilitate weight-based dosing**

DEPARTMENT OF HEALTH & HUMAN SERVICES USA
NATIONAL INSTITUTES OF HEALTH
Eunice Kennedy Shriver NICHD
National Institute of Child Health & Human Development

pSLE: recommendations

- **Develop pSLE specific disease activity measure using data collected from CARRA Registry**

JUVENILE FIBROMYALGIA

DEPARTMENT OF HEALTH & HUMAN SERVICES USA
NATIONAL INSTITUTES OF HEALTH
Eunice Kennedy Shriver NICHD
National Institute of Child Health & Human Development

Juvenile fibromyalgia: background

- **Chronic pain common in pediatrics**
  - 25% of new patients seen by pediatric rheumatologists
- **Big Three**
  - Headaches, musculoskeletal pain, abdominal pain
- **25-40% of children with chronic pain meet criteria for fibromyalgia**
- **1-6% prevalence depending on study**
- **Studies suggest long-term pain problems**

Malleson, P.N., al-Matar, M., & Petty, R.E. (1992). Idiopathic Musculoskeletal Pain Syndromes in Children. J Rheumatol, 9,1786–1789..

Buskila, D., Press, J., Gedalia, A., Klein, M., Neumann, L., Boehm, R., & Sukenik, S. (1993). Assessment of Nonarticular Tenderness and Prevalence of Fibromyalgia in Children. J Rheumatol, 20, 368–370.

Siegel, D.M., Janeway, D., & Baum, J. (1998). Fibromyalgia Syndrome in Children and Adolescents: Clinical Features at Presentation and Status at Follow-Up. Pediatrics, 101, 377–382.

Kashikar-Zuck, S., Parkins, I.S., Ting, T.V., Verkamp, E., Lynch-Jordan, A., Passo, M., & Graham, T.B.(2010). Controlled Follow-Up Study of Physical and Psychosocial Functioning of Adolescents with Juvenile Primary Fibromyalgia Syndrome. Rheumatology, 49, 2204-2209.

NATIONAL INSTITUTES OF HEALTH

Eunice Kennedy Shriver NICHD
National Institute of Child Health & Human Development

Juvenile fibromyalgia: background

- **2005 APS consensus management guidelines**
  - modifications based on the children's age, developmental level, and social environment (eg, less medication)
- ***Age-appropriate* outcome measures exist**
  - Pain, quality of life, anxiety, functional disability, etc
- **Difficulty identifying patients for studies**
  - Previously treated off-label
  - Present to a variety of specialists
  - Case definition issues
  - Overlap with other conditions

Guidelines for the Management of Fibromyalgia Syndrome Pain in Adults and Children (2005). *American Pain Society*.

Juvenile fibromyalgia: background

- **Subcommittee decided not to address purely analgesic drugs**
- **Based recommendations for study of drugs based on**
  - Proposed mechanism of action relative to proposed pathophysiology
  - Drug availability and cost, coverage by Medicaid and third-party payers
  - Lack of pediatric labeling
  - Unlikelihood of industry development

Juvenile fibromyalgia: clinical need

- **No medications labeled for use in juvenile fibromyalgia.**
- **No studies looking at drug treatment.**
- **Drugs commonly used off label in children and adolescents with fibromyalgia, particularly amitriptyline and venlafaxine**

DEPARTMENT OF HEALTH & HUMAN SERVICES USA
NATIONAL INSTITUTES OF HEALTH
Eunice Kennedy Shriver NICHD
National Institute of Child Health & Human Development

Juvenile fibromyalgia: knowledge gaps

- **Amitriptyline and venlafaxine best met the criteria the subcommittee outlined**
  - No data on efficacy of either agent in juvenile fibromyalgia
  - No good PK/PD/PG data for either agent in pediatrics
  - No data looking at the concentration of the active moiety of the parent plus the active metabolite in pediatric patients
  - Used off label in pediatric headache and abdominal pain

DEPARTMENT OF HEALTH & HUMAN SERVICES USA
NATIONAL INSTITUTES OF HEALTH
Eunice Kennedy Shriver NICHD
National Institute of Child Health & Human Development

Juvenile fibromyalgia: recommendations

- **Clinical trials testing the efficacy of amitriptyline and venlafaxine in pediatric fibromyalgia**
  - PG-aided PK study design
  - PK study on core metabolizers and extensive metabolizers