BPCA Rheumatology Therapeutic Area Working Group

Working group co-chairs:

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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
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

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<th>Disease</th>
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<td>SLE</td>
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<td>JDM</td>
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<td>Localized scleroderma</td>
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## Number of Follow Up Visits

11/26/2012

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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
IDIOPATHIC INFLAMMATORY UVEITIS
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
- JIA most frequent cause of chronic intraocular inflammation in children
  - Present in 10-20% of kids with JIA

American Uveitis society
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.


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/m²)
  - Higher doses and SC route used for uveitis
    » Optimal dose or route for treatment of uveitis not known


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?
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/m² 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
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


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?


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


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
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
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

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?


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


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
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

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
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
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.
Clinical trial comparing the safety and efficacy of IV methylprednisolone with cyclophosphamide, mycophenolate, and rituximab in pSLE-induced seizures and cerebral vascular events
  - Utilize interferon signature, other biomarkers as well as standard clinical outcome measures

Support for CARRA CTPs comparing corticosteroid dosing regimens
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
pSLE: recommendations

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


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
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.
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
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