Past, Present and Future of Clinical Research in Pediatric Rheumatology

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Objectives

1. To describe the evolving nature of clinical research in pediatric rheumatology, using juvenile arthritis as example

2. To highlight the role of collaborative research networks
Today’s presentation

• The case:
  – What will happen to my child?
• The past
• The present
• The future
• Back to the case and wrap up
The case

- A.D., a three year old previously healthy girl presents with a right-sided limp for 3 months
- On exam, swelling and limited range in knee, ankle and both wrists.
- X-ray and blood work unremarkable
The case

• You give the bad news:
  – Your child has arthritis

• They ask:
  – Doctor, what will happen to my child?
  – What treatment will be needed?

• You scratch your head and reflect:
  – What you said yesterday
  – What can you say today
  – What you might say tomorrow
The past

• Your child has a debilitating disease with no cure
• No medication has ever been properly tested (in a RCT) for this condition
• We can’t even agree on how to call this disease
• We will start treatment with high-dose aspirin and see how things go
The past
The past

- Prognosis and treatment based on case series and adult trials
- Disease called juvenile rheumatoid arthritis on this side of the Atlantic and juvenile chronic arthritis on the other side.
- Current criteria for juvenile idiopathic arthritis (JIA) published in 2004
- First properly-sized randomized controlled trials published around 1985
The case – present

- A.D., a three year old girl with newly diagnosed arthritis
- Parents ask:
  - Doctor, what will happen to my child?
  - What treatment will be needed?
• Your child has JIA
• >80 % of children with this JIA subtype (oligoarthritis), are fully controlled with treatment
• Best initial treatment is with NSAIDs and joint injections
• If this doesn’t work, DMARDs and biologic agents are effective (RCTs)
The present

• International agreement on JIA definition and subtypes:
  – oligoarthritis (40-60%), polyarthritis RF- (10-25%), polyarthritis RF+ (5-10%), enthesitis-related (3-10%), systemic (5-15%), psoriatic (2-10%), undifferentiated (10-20%)

• Prognosis based on several large inception cohorts

• Treatment informed by > 100 trial reports

Petty et al, J Rheumatol 2004
How did we get here?

- Two major clinical research advances:
  - Multicentre longitudinal inception cohorts
  - Multicentre randomized clinical trials
- In essence: collaborative clinical research networks
- Similar to networks in other areas of pediatrics, but mostly investigator driven
- Basic research advances, biologic agents
Collaborative networks

• Pioneers: The U.S.A.—U.S.S.R. collaborative clinics
• Pediatric Rheumatology Collaborative Study Group (PRCSG)
• Pediatric Rheumatology International Trials Organization (PRINTO)
• Canadian Association of Pediatric Rheumatology Investigators (CAPRI)
Multicentre cohorts vs. case series

Cohorts:
- Many centres, generalisable
- Defined data collection
- Prospective data entered in database
- Few years to collect enough sample
- Standard self-report measures

Case series:
- One centre, limited generalisability
- Usual charting
- Retrospective extraction of data
- Many years to collect enough sample
- No self-report available
ReACCh-Out

• Research in Arthritis in Canadian Children emphasizing Outcomes (ReACCh-Out).
• Pan-Canadian project of pediatric rheumatology centres (CAPRI) funded by CIHR
• Follows course and outcomes of >1500 children with JIA
• Every 6 months core data set:
  – joint counts, functioning, parent and physician global assessment, quality of life, inflammatory markers, disease features, treatment requirements
ReACCh-Out findings

- With current treatments, the percentage of children with inactive JIA (all subtypes) increases from 5% at enrollment to 33% at 6 months, and 49% at 24 months.
- >50% of children with oligoarthritis were fully functional and had no detectable disease within 6 months.
Analysis challenges
Trials in JIA

• > 14 trials of anti-inflammatory agents
• > 14 trials of non-biologic DMARDs
• > 5 trials of biologic agents
• 3 trials of corticosteroid injections

• Challenges in data analysis
• Unique randomized withdrawal trials

Haskes & Laxer, JAMA 2008
Analysis of RCT’s

• Follow subjects on treatment A or treatment B for two years
  – See how they end
  – See how they change from baseline to end
  – See how they do during the full study
Traditional RCT

Effect of drugs A and B on function

CHAQ score

Months on treatment

Drug A

Drug B
Randomized withdrawal trial

- All children start on active drug
- Responders are randomized to continue drug or switch to placebo
- Children who flare on placebo go back on drug
- Open long-term follow-up
Randomized withdrawal trial

% improved vs. Months on treatment
The case – future

• A.D., a three year old girl with newly diagnosed arthritis

• Parents ask:
  – Doctor, what will happen to my child?
  – What treatment will be needed?
The future

• Based on her genetic, biological and clinical markers, your child has a 90% chance of full remission within 2 years and 60% chance that it will never come back (cured?).

• The best initial treatment for her is A, followed by B+C.

• We will avoid D since it has a high risk of side effects in your child.
The future

- Genetic markers
- Biological markers
- Clinical prediction
- Collaborative trials of treatment paths instead of single drugs
- Real-time monitoring of function
- Oral “biologic” agents targeted to mediator signal transduction
The LEAP project

- Linking Exercise, Activity and Pathophysiology in JIA (LEAP)
- Team grant funded by CIHR (about half a million per year)
- Collaboration of researchers in rheumatology (CAPRI), physical activity and rehabilitation, biomarkers, bone and muscle development
- Longitudinal measurement of physical activity, disease activity, biomarkers, bone structure and muscle strength in JIA cohorts
LEAP conceptual model

Successful PA intervention

↑ Physical activity (exercise)

↑ Physical activity (exercise)

↑ Muscle strength

↑ Bone strength

Damage to joints

↑ Development and growth

↑ Quality of life

↑ Functional ability

↓ Disease activity (inflammation)

↓ Pain

↓ Fatigue

↑ Opportunities for PA

↑ Family modeling of PA

Perceived barriers for PA

↓ Self efficacy for exercise

Cultural and societal factors

Successful drug therapy

Physical activity (exercise)

Disease activity (inflammation)

Successful PA intervention

↑ Bone strength

↑ Development and growth

↑ Quality of life

↑ Functional ability

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Measuring What Counts

- 20 children with JIA monitored one week before and one week after joint injection
- Electronic tracking of physical activity and community participation via iPhone and accelerometer
- To test feasibility of monitoring in cohorts and as outcome measure in trials
UCAN

- Understanding Childhood Arthritis Network
- International collaboration of cohorts of children with JIA (Meta-Cohorts)
- To elucidate genetic markers explaining disease phenotype heterogeneity

From: bluegiant.com
Back to the case – wrap up

• A.D., a three year old girl with newly diagnosed JIA

• Parents ask:
  – Doctor, what will happen to my child?
  – What treatment will be needed?
In summary

- Pediatric rheumatology has seen major changes in how clinical research is done.
- Multicenter inception cohorts and randomized withdrawal trials have advanced prognosis and treatment of JIA.
- How do we answer parents’ questions is changing and the future is bright.
- Clinical epidemiology challenges remain in deciding how best to analyze information.
Past, present, future
Thank you. Any questions?