Case example:

Drug-Class Specific Extrapolation for Juvenile Idiopathic Arthritis: TNFα Inhibitors

Satjit Brar Pharm.D., Ph.D.
Team Leader – Office of Clinical Pharmacology

CERSI Pediatric Drug Development: Use of Exposure Matching and Exposure-Response for Extrapolation of Efficacy in Pediatric Product Development

Disclaimer

Opinions expressed in this presentation are those of the speaker and do not reflect official positions or policies of the FDA. No official endorsement by the FDA is intended or should be inferred.

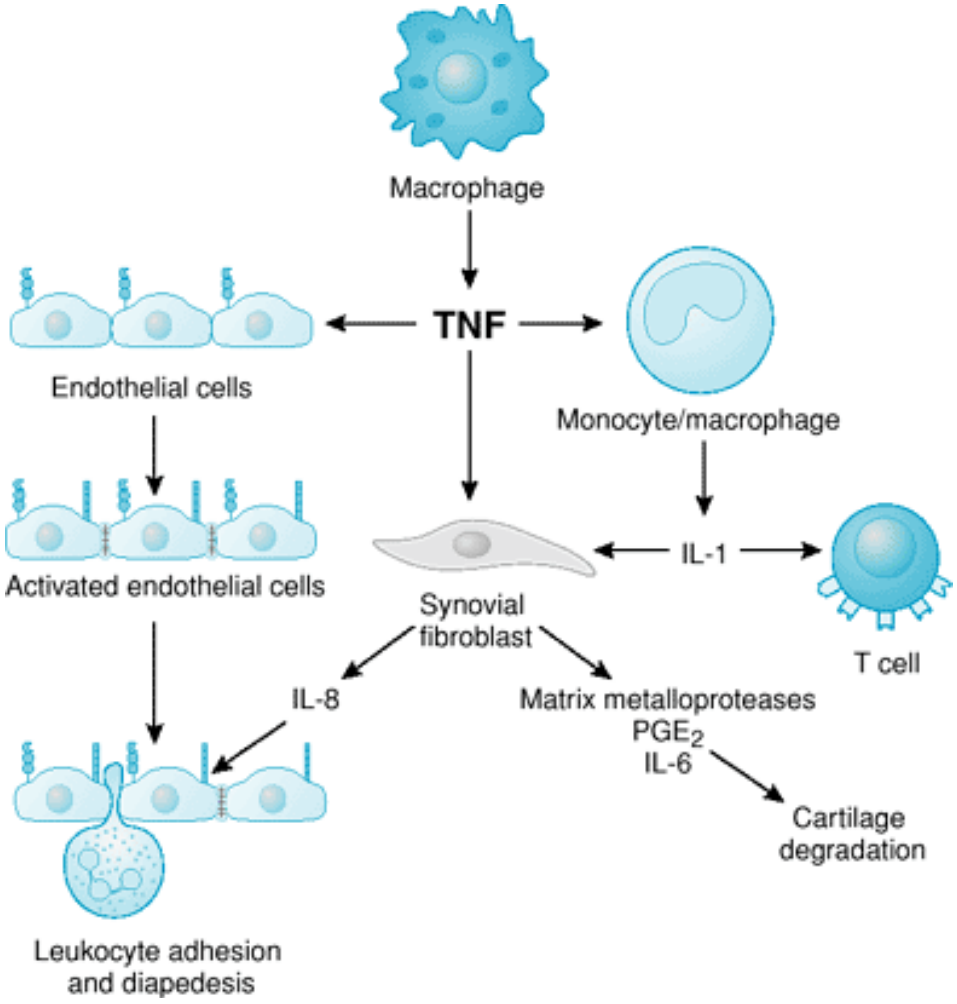
Premise

- We have enough clinical investigational experience with the TNFα inhibitors in poly-articular JIA (pJIA) to extrapolate efficacy from adult Rheumatoid Arthritis (not been implemented as yet).
- Efficacy is extrapolated from adult rheumatoid arthritis to the poly-articular subtype of JIA, because this subtype most resembles rheumatoid arthritis.

Are we ready to extrapolate?

- What qualitative/quantitative information do we need to show ability to extrapolate for other drug classes?

TNF-α Inhibitors in RA



- TNFα Inhibitors
  - Enbrel (etanercept)
  - Remicade (infliximab)
  - Humira (adalimumab)
  - Simponi (golimumab)
  - Cimzia (certolizumab)
- IL-1 inhibitors
  - Kineret (anakinra)
- T-cell Costim Mod
  - Orencia (abatacept)
- Anti-CD20
  - Rituxan (rituximab)
- IL-6 inhibitors
  - Actemra (tocilizumab)

Arthritis in Children - Classification

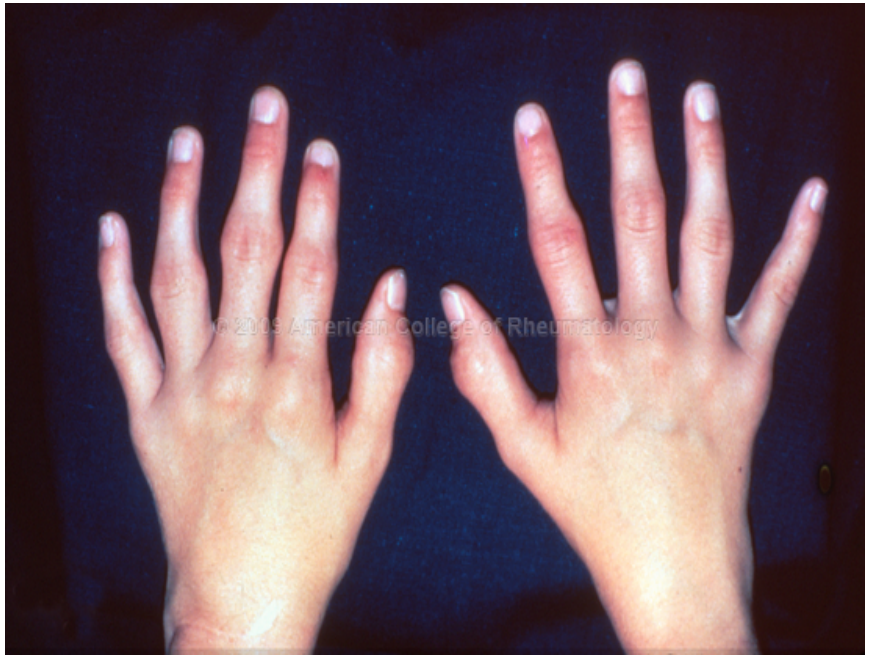
ACR (1977) JRA	EULAR (1978) JCA	ILAR (2001) JIA
Systemic	Systemic	Systemic
Polyarticular	Polyarticular	Polyarticular RF–negative
Pauciarticular	Pauciarticular	Polyarticular RF–positive
	Juvenile psoriatic	Oligoarticular
	Juvenile ankylosing spondylitis	Persistent
	Arthritis associated with inflammatory bowel disease	Extended
		Psoriatic
		Enthesitis-related
		Undifferentiated

ACR, American College of Rheumatology; JRA, juvenile rheumatoid arthritis; EULAR, European League Against Rheumatism; JCA, juvenile chronic arthritis; ILAR, International League of Associations for Rheumatology; JIA, juvenile idiopathic arthritis; RF, rheumatoid factor.

Update on Pediatric Rheumatology, 2012

Poly-articular Juvenile Idiopathic Arthritis (pJIA)

- JIA is defined as persistent arthritis for more than 6 wks, with onset <16 yrs of age and the prevalence rate of ~294,000 in the US
- pJIA is JIA with five or more joints during the first 6 months
- pJIA is considered the juvenile equivalent of RA
- RA approvals trigger a PREA requirement to study PJIA



images.rheumatology.org

Pharmacotherapy of pJIA

- Demonstrated Efficacy in pJIA
  - NSAIDs
    - Naproxen, Oxaprozin, Meloxicam, Etodolac
  - COX2 inhibitors
    - Celecoxib, Rofecoxib
  - DMARDs
    - Methotrexate, Sulfasalazine
  - Biologics
    - **Etanercept, Adalimumab** Abatacept
  - Corticosteroids

- Failed Demonstrating Efficacy in pJIA
  - DMARD
    - Leflunomide
  - TNF inhibitor
    - **Infliximab**

- TNF inhibitors under evaluation for pJIA
    - **Golimumab**
    - **Certolizumab**

Case 1: Enbrel (Etanercept)

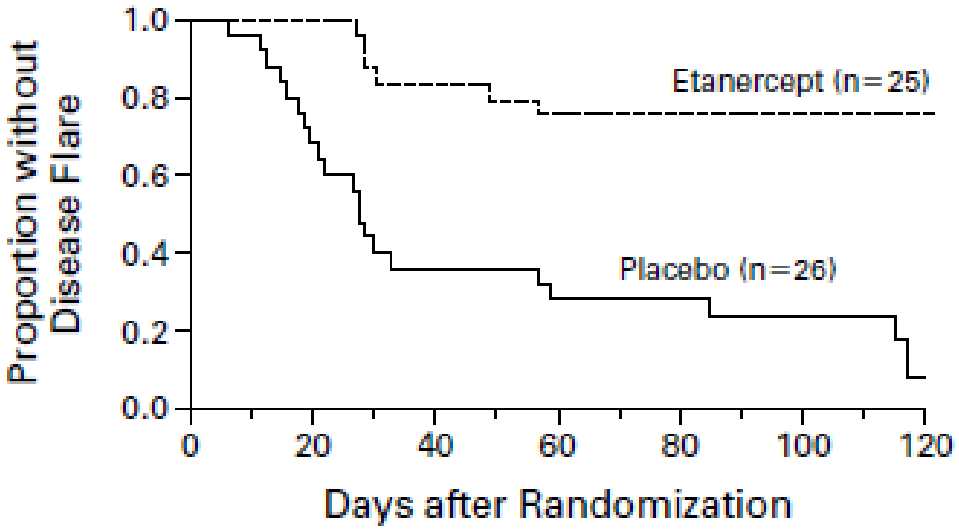
- Mechanism of action: Blocking TNFα effect (fusion protein)
- Dosing and administration:
  - Adult dosing for RA indication: 50 mg SC once weekly
  - Pediatric dosing was approved half-year later after the original submission

Etanercept Pediatric Trial

- Objectives: Efficacy, safety and PK
- Patients: pJIA patients 4-17 years, N=69
- Design: Open-label lead in phase followed with a 4-month randomized double-blind phase
- Primary endpoint: Time to disease flare
- Dosing regimen:
  - Placebo
  - Etanercept: 0.4 mg/kg up to 25 mg SC twice weekly

Etanercept Trial Results

Efficacy



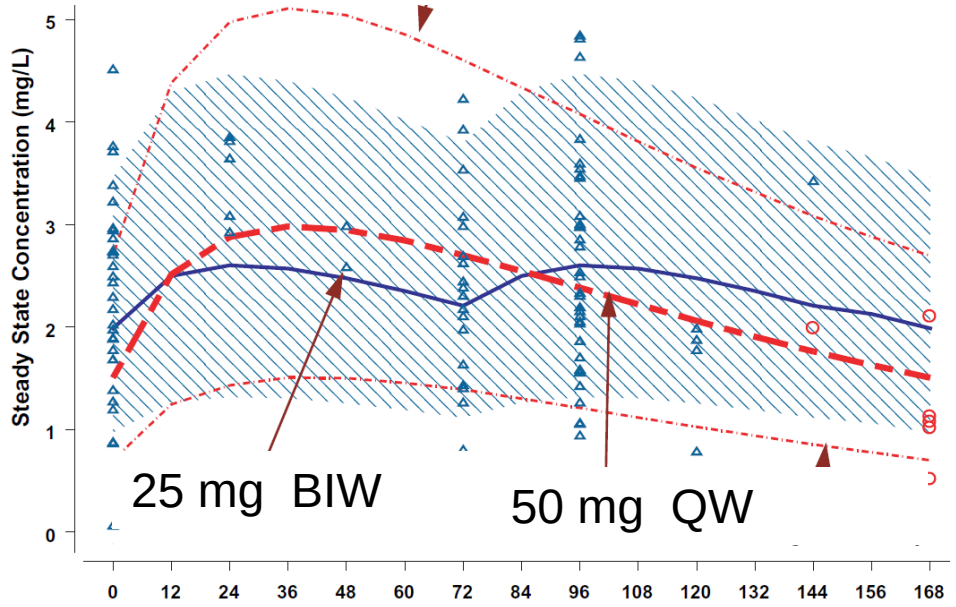
Etanercept group significantly better than placebo for efficacy, comparable for safety

Safety

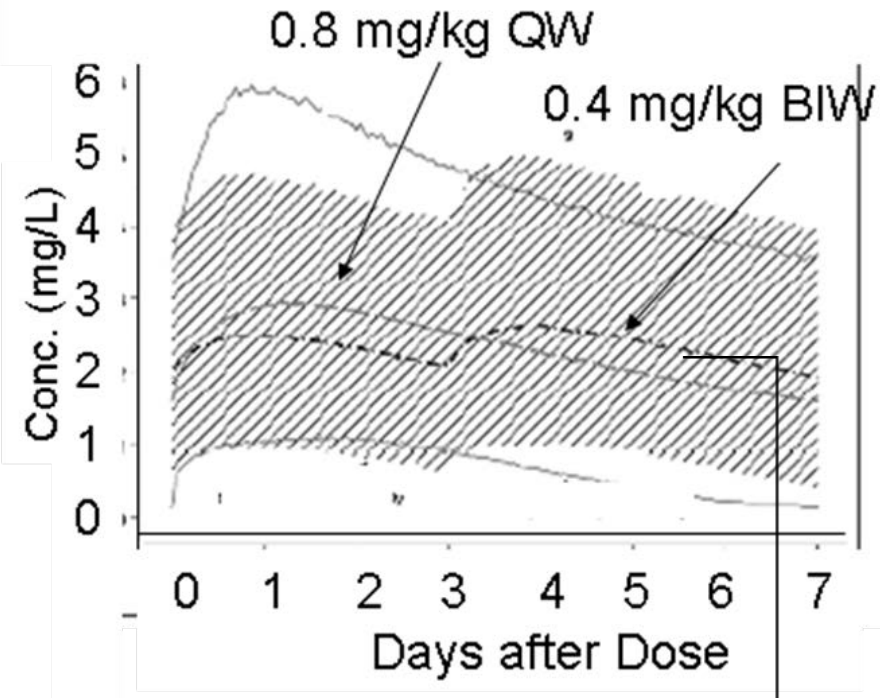
- Well tolerated
- No significant differences in the frequencies of adverse events between patients who received etanercept and those who received placebo.

Etanercept Exposures Adults versus pJIA

ADULT RA



pJIA



Efficacy trial

0.4 mg/kg BIW approved for PJIA

0.8 mg/kg QW approved for PJIA

Lee, 2005

Case 2: Remicade (Infliximab)

- Mechanism of action: Blocking TNFα effect
- Dosing and administration:
  - Adult dosing for RA indication: 3 mg/kg IV at 0, 2 and 6 weeks, then every 8 weeks
  - Pediatric dosing was not approved during the original submission
- PREA required to assess the pediatric safety and efficacy

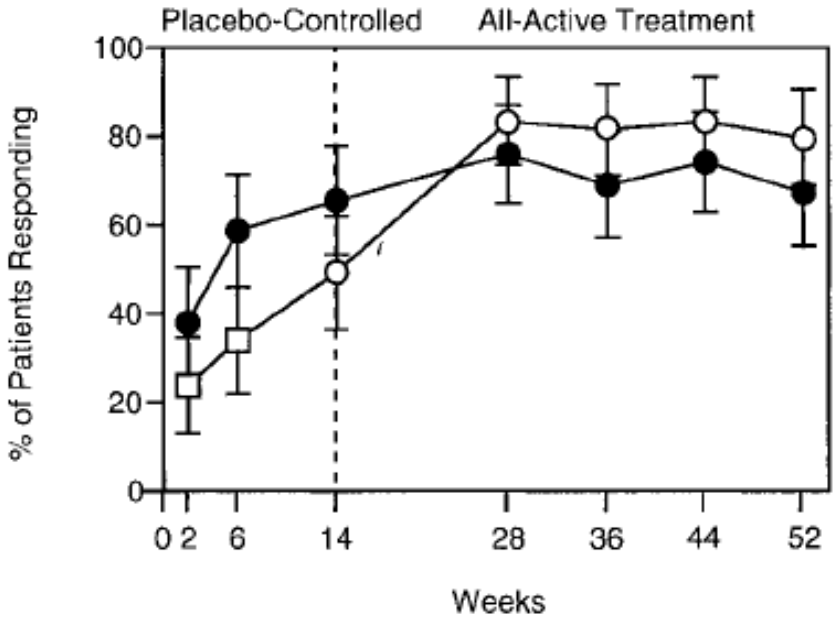
Ruperto, 2007

Infliximab Pediatric Trial

- Objectives: Efficacy, safety and PK
- Patients: PJIA patients 4-17 years, N=122
- Design: 14-week, randomized, double-blind, active-controlled study, followed by a double-blind, all-active treatment extension
- Primary endpoint: JRA-30 DOI at week 14
- Dosing regimen:
  - Placebo: placebo + MTX at weeks 0, 2, and 6, followed by an infliximab 6 mg/kg + MTX at weeks 14, 16, and 20 and then every 8 weeks
  - Infliximab: 3 mg/kg + MTX at weeks 0, 2, 6, 14, 20 and then every 8 weeks

Infliximab Trial Results

Efficacy



The between-group difference in this primary efficacy end point was not statistically significant for 3 mg/kg and placebo.

Safety

- generally well tolerated
- safety profile of infliximab 3 mg/kg appeared less favorable than that of infliximab 6 mg/kg,
- more frequent occurrences of serious adverse events, infusion reactions, antibodies to infliximab, and others.

Infliximab Pediatric Decisions

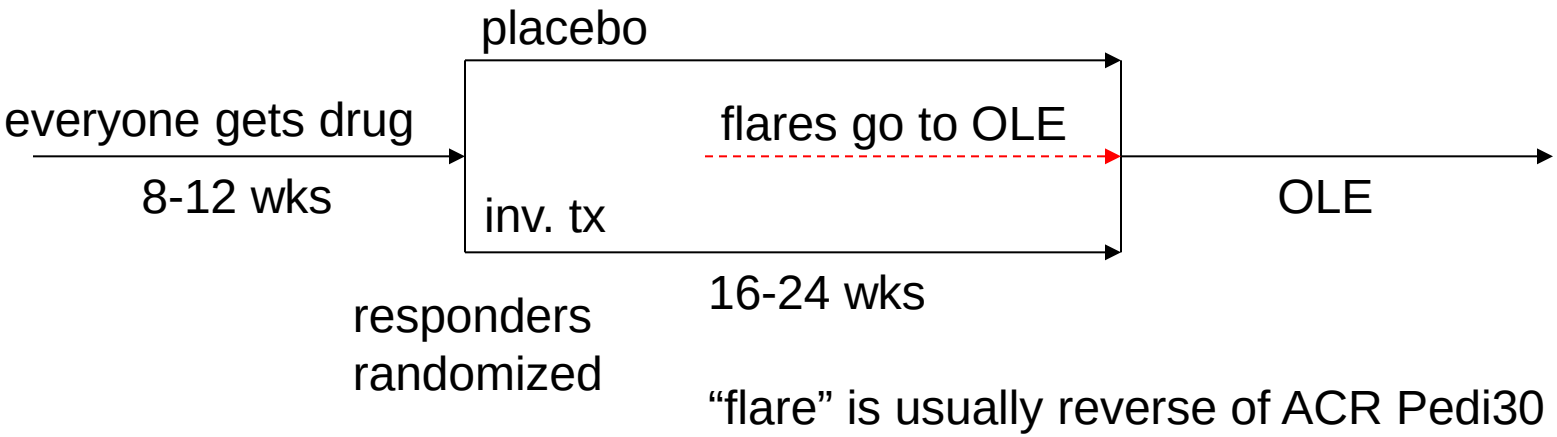
- Not indicated for pJIA use
  - High placebo response
  - High rate of immunogenicity
  - Higher clearance in pediatric patients

General trial design for pJIA

– Randomized withdrawal

Considered more palatable because all patients receive active treatment

PK match



"flare" is usually reverse of ACR Pedi30 response

Endpoint is usually the proportion of patients experiencing a flare during the withdrawal period. Time to flare may be used alternatively

Discussion

- Evidence for extrapolation:
  - We will have enough clinical investigational experience with the TNFα inhibitors in pJIA (will be n=5 pediatric trials)
  - pJIA subtype most resembles rheumatoid arthritis.
  - Besides this, what additional information would be useful in determination of the ability to extrapolate?

- What qualitative/quantitative information do we need to show ability to extrapolate for other drug classes?