Considerations for Adult RA and JIA Drug Development through the Quantitative Assessment of Disease Comparisons

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Outline

• Background on Tocilizumab
• Comparison of pJIA and Adult RA
  – Disease characteristics
  – Clinical trial considerations
  – Dosing and route of administration
• JIA and Growth
**Tocilizumab (TCZ): Humanized Anti–IL-6R mAb**

**Mouse**

- **Fab**

**Fc**

**Antigenicity in humans**

- ++

**Chimeric**

- +

**Humanized**

- ±

CDR, complementarity-determining regions; Fab, fragment antigen-binding region; Fc, fragment crystallizable region; IL-6R, interleukin-6 receptor; mAb, monoclonal antibody; TCZ, tocilizumab.

Current FDA approved indications for TCZ (Actemra)

INDICATIONS AND USAGE

ACTEMRA® (tocilizumab) is an interleukin-6 (IL-6) receptor antagonist indicated for treatment of:

Rheumatoid Arthritis (RA) (1.1)
• Adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more Disease-Modifying Anti-Rheumatic Drugs (DMARDs).

Polyarticular Juvenile Idiopathic Arthritis (PJIA) (1.2)
• Patients 2 years of age and older with active polyarticular juvenile idiopathic arthritis.

Systemic Juvenile Idiopathic Arthritis (SJIA) (1.3)
• Patients 2 years of age and older with active systemic juvenile idiopathic arthritis.
Actemra (Tocilizumab) Development History

ACTEMRA: A DECADE OF CLINICAL STUDY EXPERIENCE
PIVOTAL PHASE III STUDIES & APPROVED INDICATIONS

*Includes 9 pivotal Phase III studies; additional trials not shown.
What Is Juvenile Idiopathic Arthritis (JIA)?

- JIA is a group of arthritides of unknown etiology that begins in children younger than 16 years and persists for >6 weeks’ duration\(^1,\)\(^a\)
- Prevalence of JIA varies between 16 and 150 cases per 100,000 children\(^2\)
- JIA is rare and classified into subtypes after 6 months of disease

Frequencies are percentages of all JIA.

\(^a\)The classification of juvenile idiopathic arthritis was modified in 2001 by ILAR.

## Comparison of RA and JIA

<table>
<thead>
<tr>
<th>Feature</th>
<th>RA</th>
<th>JIA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Classification Criteria</td>
<td>Single disease with different</td>
<td>Phenotypically and genetically distinct</td>
</tr>
<tr>
<td></td>
<td>manifestations</td>
<td>distinct subtypes</td>
</tr>
<tr>
<td>Gender</td>
<td>F&gt;M</td>
<td>F&gt;M except sJIA</td>
</tr>
<tr>
<td>Age of Onset</td>
<td>Peak 4&lt;sup&gt;th&lt;/sup&gt; to 5&lt;sup&gt;th&lt;/sup&gt;</td>
<td>Throughout childhood with different</td>
</tr>
<tr>
<td></td>
<td>decade</td>
<td>peaks of age dependent on subtype</td>
</tr>
<tr>
<td>Typical ocular involvement</td>
<td>Keratoconjunctivitis sicca</td>
<td>Chronic anterior uveitis</td>
</tr>
<tr>
<td>Prevalence</td>
<td>10/1000</td>
<td>0.9/1000</td>
</tr>
<tr>
<td>Ethnic distribution</td>
<td>All populations</td>
<td>Early onset oligo JIA is rare in non-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Caucasians</td>
</tr>
<tr>
<td>HLA association</td>
<td>HLA DRB1 0401, 0404, 0101 in Caucasians</td>
<td>Oligo – HLA-A2, -DR5, -DR8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>pJIA – HLA-DR1, -DR4</td>
</tr>
<tr>
<td>Growth/development issues</td>
<td>Rare</td>
<td>Common</td>
</tr>
<tr>
<td>Autoantibodies</td>
<td>IgM RF common</td>
<td>IgM RF rare</td>
</tr>
<tr>
<td>Natural history</td>
<td>Large proportion have long-term</td>
<td>Long-term disability relatively</td>
</tr>
<tr>
<td></td>
<td>disability</td>
<td>rare.</td>
</tr>
</tbody>
</table>

Adapted from Arthritis Research & Therapy 2002;4(Suppl 3):303
Similar Cytokines Are Major Mediators of JIA and RA Pathogenesis\textsuperscript{1-7}

\textsuperscript{a}In human hepatocytes, IL-6 is the major regulator of CRP and hepcidin.

Polyarticular course JIA subtypes most similar to Adult RA

- Polyarticular course JIA subtypes

**Similarities to adult RA**
- Clinical course
- Presence of peripheral joint synovitis
- Response to therapeutic agents e.g., Methotrexate, Anti-TNFα

* As recommended in FDA RA guidance 1999
Clinical Trial Considerations
Adult RA: Example Phase III Study Designs

**SUMMACTA non-inferiority study**

**Primary end point**
- ACR20 response at 24 weeks (noninferiority margin, 12%)

**BREVACTA superiority study**

**Primary end point**
- ACR20 response at 24 weeks

**Secondary end point**
- Change from baseline in van der Heijde modified Sharp radiographic score to Week 24 and to Week 48
Patients who completed part 1 with ≥JIA ACR30 response were eligible to enter part 2.

Withdrawal Design and the Pediatric Study Population

“There is intense debate about placebo-controlled studies among ethics committees/IRBs, practitioners, and families, any of which may reject such studies due to the prospect of a child with active JIA being assigned to receive placebo for several weeks or months”

Advantages of Withdrawal Design:

• All subjects receive experimental treatment
• Escape therapy limits exposure to placebo to responders only
• Minimization of exposure to ineffective medical treatment
• Open-label phase more closely approximates routine clinical care

Other Considerations:

• Bias towards responders
• Limited patient-year exposure on placebo
• Not practical for treatments with long duration of biologic effect
• For sample size, different JIAs (RF+, RF- and OE) grouped as “single” JIA category
The ACR Core Components for Adult RA and JIA are generally comparable

These components for the basis of the ACR and JIA ACR endpoints that are the foundation of assessment of response to therapeutic agents in Adult RA and JIA

<table>
<thead>
<tr>
<th>ACR Core Components</th>
<th>JIA ACR Core Components</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tender Joint Count</td>
<td>Number of joints with active arthritis</td>
</tr>
<tr>
<td>Swollen Joint Count</td>
<td>Number of joints with limited range of motion</td>
</tr>
<tr>
<td>Patient assessment of pain</td>
<td>N/A</td>
</tr>
<tr>
<td>Patient assessment of disease activity</td>
<td>Parent/patient assessment of overall wellbeing</td>
</tr>
<tr>
<td>Physician assessment of disease activity</td>
<td>Physician assessment of disease activity</td>
</tr>
<tr>
<td>Patient assessment of Physical Function</td>
<td>Parent/patient assessment of Physical Function</td>
</tr>
<tr>
<td>Acute Phase Reactants</td>
<td>Acute Phase Reactants</td>
</tr>
</tbody>
</table>
Tocilizumab in Adult RA
DMARD Inadequate Responders: ACR20, ACR50, ACR70
Response Rates at Week 24. Pooled, ITT Population

Recommended Intravenous (IV) Dosage Regimen:

The recommended dosage of ACTEMRA for adult patients given as a 60-minute single intravenous drip infusion is 4 mg per kg every 4 weeks followed by an increase to 8 mg per kg every 4 weeks based on clinical response.
CHERISH (pcJIA): Efficacy in Part 1—JIA ACR Responses

Recommended Intravenous PJIA Dosage Every 4 Weeks

<table>
<thead>
<tr>
<th>Patients</th>
<th>Dosage</th>
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<tbody>
<tr>
<td>less than 30 kg weight</td>
<td>10 mg per kg</td>
</tr>
<tr>
<td>at or above 30 kg weight</td>
<td>8 mg per kg</td>
</tr>
</tbody>
</table>
Adult DAS28 and JIA JADAS71 Comparison

DAS28

\[\text{DAS28} = 0.56 \times \sqrt{\text{tender28}} + 0.28 \times \sqrt{\text{swollen28}} + 0.70 \times \ln(\text{ESR}) + 0.014 \times \text{Patient Global (10cm VAS)}\]

\(<2.6 \text{ (remission)}\)
\(\leq 3.2 \text{ (low disease activity)}\)
\(>5.1 \text{ (high disease activity)}\)

JADAS71

\[\text{JADAS71} = \text{Active Joint Count} + \text{Physician Global (10cm VAS)} + \text{Parent Global (10cm VAS)} + \text{ESR}\]

\(<3.8 \text{ (minimal disease activity)}\)
\(<1.0 \text{ (inactive disease)}\)
At week 104:
- 73.2% patients with JADAS-71 < 3.8 (minimal disease activity)
- 58.5% patients with JADAS-71 < 1.0 (inactive disease)

Each visit included patients with a nonmissing assessment at the time point.
Patients who previously withdrew were excluded. JADAS-71 cutoffs derived from Consolaro A et al. *Arthritis Rheum.* 2012;64:2366.
(DAS28) by Visit up to week 52 – Adult RA – DMARD-IR

% patients in DAS remission (<2.6) at week 52:
Placebo 7.9
4mg/kg Actemra 30.2
8mg/kg Actemra 47.2

Missing data: LOCF for SJC abd TJC; no imputation for ESR and patient's global assessment; excl. escape
Joint Progression Comparison RA and JIA

Adult RA
Modified Total Sharp Scores

JIA
Modified Total Sharp Scores + Poznanski Score*

*carpometacarpal ratio
Dosing Considerations for pcJIA
Dose Rationale for pcJIA (Modeling & Simulation)

Dosing Pediatric Patients with pJIA with Low Body Weight (< 30 kg) with TCZ IV 10 mg/kg could Improve Uniformity of Exposure

tocilizumab exposure versus body weight after 6 months of treatment (8 mg/kg or 10 mg/kg) in Japanese JIA patients (n=19)

- ≥30kg – 8mg/kg
- <30kg – 10mg/kg
- <30kg – 8mg/kg

Body Weight (kg)

tocilizumab AUC (µg/mL*d)

BW > 40 kg (N= 7)
BW 30-40 kg (N= 4)
BW 20-30 kg (N= 3)
BW < 20 kg (N= 5)
Results from Roche pcJIA study (CHERISH) confirmed Dosing Rationale

$C_{\text{trough}}$ and AUC of the 10mg/kg <30kg patients are Comparable with 8mg/kg ≥ 30kg patients
IV to SC Pediatric Bridging Summary
JIGSAW Study (WA28117) for SC TCZ in pcJIA: PK/PD Bridging Approach

**GOAL:** To establish a SC TCZ dosing regimen for a fixed dose across the wide range of bodyweights encountered in pediatric patients with pJIA

- A 52 week phase Ib, open-label, multi-center study to investigate pharmacokinetics, pharmacodynamics and safety of SC TCZ SC in pJIA
- Analogous bridging approach being used for SC TCZ in sJIA (WA28118)
- PK sampling prioritized due to blood volume considerations (especially in youngest enrolled 1-2 year old children)

**STUDY OBJECTIVES**

- To evaluate PK/PD of SC TCZ in patients with pJIA
- To evaluate the safety of SC TCZ in patients with pJIA
- Efficacy of the SC TCZ formulation is included as an exploratory objective

**Pre-planned interim analysis** to evaluate dosing regimens conducted once approximately 24 patients had completed the first 14 weeks of the study
Pre-study modeling simulations suggest that protocol dosing regimens allow patients to achieve the targeted level of exposure (Cmin) in both dosing groups.

- **pJIA IV**
  - 8 mg/kg IV Q4W for BW ≥ 30kg
  - 10 mg/kg IV Q4W for BW < 30kg

- **pJIA SC**
  - 162 mg Q2W for SC BW ≥ 30kg
  - 162 mg Q3W for SC BW < 30kg
SC TCZ dosing regimens of Q3W in <30 kg patients and Q2W in ≥30 kg patients bridge IV dosing exposures in each weight group
Dosing regimens continued unchanged after interim analysis

**PREDICTED:**
- 162 mg SC Q2W  BW ≥ 30kg
- 162 mg SC Q3W  BW < 30kg

**AT INTERIM ANALYSIS:**
- 162 mg SC Q2W  BW ≥ 30kg
- 162 mg SC Q3W  BW < 30kg
JIGSAW Study (WA28118) for SC TCZ in sJIA: Interim Analysis Data

SC TCZ dosing regimen of QW in ≥30 kg patients bridges IV dosing exposures but Q10D dosing regimen in <30 patients gave higher exposures than IV dosing.

Dosing frequency for <30 kg patients reduced to Q2W after interim analysis and additional patients recruited into study to evaluate new dosing regimen.

### INTERIM ANALYSIS:

- **162 mg SC QW**  BW ≥ 30kg
- **162 mg SC Q10D** BW < 30kg

### PREDICTED:

- **162 mg SC QW**  BW ≥ 30kg
- **162 mg SC Q10D** BW < 30kg
Growth and JIA
CHERISH (pJIA) Growth: Height Velocity at Year 2 Versus Baseline Age

- Mean height SDS higher than for sJIA patients in TENDER (-0.5 vs -2.2)
- Patients experienced excellent growth during 2 years of TCZ treatment

Solid black curves represent the expected height velocity based on WHO norms for height for the mean observation time.
84 patients were randomly assigned to receive placebo treatment during the part 2 withdrawal phase; fewer than half the patients received placebo through the entire 24 weeks of part 2 because most escaped to TCZ before week 40.

Bharucha KN et al. ACR; November 14-19, 2014; Boston, MA
Bharucha KN et al 2016, manuscript in preparation
sJIA Growth: Poor Pre-treatment Height Velocity

- sJIA study population with short stature at baseline (mean height SDS = -2.2)
- For patients with pre-trial height data, pre-treatment height velocities were below age-adjusted averages in 87.5% of the female patients and 89% of the male patients.

X axes show patient age at baseline. Dots represent individual patients. Curves represent the expected height velocities during the year before baseline based on WHO norms.
sJIA Growth: Improved at Week 104 of Treatment

- Patients experienced catch-up growth during 2 years of TCZ treatment
- In patients with pre-trial height data, height velocities of 83% of female patients (n = 24) and 73% of male patients (n = 19) were now above expected age-adjusted averages

X axes show patient age at baseline.
Dots represent individual patients.
Curves represent the expected 2-year annualized height velocities based on WHO norms.

Summary and Conclusion

• Juvenile Idiopathic Arthritis has many distinct subtypes of disease
• Polyarticular course JIA is the most similar to adult RA in terms of phenotype and response to therapeutic agents
• Targeting common pathways between pJIA and RA is important in allowing direct extrapolation of data
• Direct Extrapolation of data from adult RA to pJIA does however require that consideration be given for differences in:
  – Clinical study design
  – Differences in components of response measures & magnitude of response
  – Relative importance of x-ray progression vs skeletal growth
• Consideration for differences in dosing between adult RA and pJIA:
  – The influence of bodyweight
  – Route of administration considerations, SC vs IV
  – Utility of modeling and simulation & interim analysis to predict dosing
Doing now what patients need next