TRial of Early Aggressive Therapy in Juvenile Idiopathic Arthritis

TREAT  JIA

NCT 00443430

Authors

Principal Investigator: Carol Wallace (Seattle Children's Hospital)
Co–PIs: Ed Giannini and Dan Lovell (Cincinnati Children's Hospital)

Site Principal Investigators
- Steven Spalding, Philip Hashkes (Cleveland Clinic Foundation)
- Kathleen O’Neil (Oklahoma University Health Science Center)
- Andrew Zelt (University of Utah)
- Iona Szef (Rady Children’s Hospital, San Diego)
- Sarah Ringold (Seattle Children’s Hospital & Research Institute)
- Hermine Brunner (Cincinnati Children’s Hospital Medical Center)
- Laura Schanberg (Duke University Medical Center)
- Robert Sundel (Children’s Hospital of Denver)
- Diana Milojeric (University of California, San Francisco)
- Marilyn Punaro (Texas Scottish Rite Hospital)
- Peter Chira (Stanford University School of Medicine)
- Beth Gottlieb (Schneider Children’s Hospital)
- Gloria Higgins (Nationwide Children’s Hospital)
- Norman Ilowite (Children’s Hospital of Montefiore)
- Yukiko Kimura (Hackensack University Medical Center)

Study Staff: Stephanie Hamilton, Anne Johnson, Bin Huang

Disclosures

Carol Wallace: Amgen, Bristol-Meyers Squibb, Genentech, Pfizer
Daniel Lovell: Abbott Pharmaceuticals, Bristol-Meyers Squibb, Centocor, Hoffmann-La Roche, UBC
Norm Ilowite: Centocor, Genentech
Yukiko Kimura: Genentech
Laura Schanberg: Pfizer

Amgen supplied etanercept and etanercept placebo

References


Rationale for this Study

• Children with polyarticular JIA comprise approximately 30% of those with JIA, require chronic medications and often have a poor outcome
• The most effective treatment for JIA is not known
• Aggressive therapy has been shown to result in superior outcomes in adults with rheumatoid arthritis
• There appears to be a “window of opportunity” early in the course of RA during which therapy can change the rate of progression of the disease
• These concepts have not been demonstrated or investigated in children with JIA using a double-blind, placebo controlled, randomized trial

Study Objectives

Primary Objective:
To determine if two different aggressive treatment regimens begun early in the course of poly JIA can induce Clinical Inactive Disease within 6 months of treatment

Secondary Objectives:
• Determine the safety profile of the two aggressive treatment arms
• Observe the change in the ACR Pediatric core set variables
• Determine the proportion of patients who achieve Clinical Remission on Medication by 12 months
Methods

• Randomized, double blind, placebo controlled comparison of two aggressive treatment arms
• 85 patients with new onset poly JIA from 15 sites
• NIH- NIAMS funded RO1 AR049762
• Treatment length up to 12 months
• Patients seen at 0, 2, 4, 5, 6, 7, 8, 10, 12 months with clinical and lab assessments at every visit, including a blinded joint exam
• Serum, plasma, PBMCs, and RNA stored at baseline, 4, 6 and 12 months; DNA at 2 months

Validated Criteria for Study Outcomes

Clinical Inactive Disease (CID) in JIA
• No joints with active arthritis
• No fever, rash, serositis, splenomegaly, or generalized lymphadenopathy attributable to JIA
• No active uveitis
• Normal ESR
• Physician’s global assessment of disease activity of 0, indicating no disease activity

Clinical Remission on Medication (CRM)
Clinical Inactive Disease for a period of at least 6 continuous months on medication

ACR Pediatric Core Set

• Physician global assessment of disease activity
• Parent/patient assessment of overall well-being
• Functional ability (Childhood Health Assessment Questionnaire)
• Number of joints with active arthritis
• Number of joints with limited range of motion
• Lab measure of acute inflammation (ESR)

ACR Pediatric 70 responder:
• ≥ 70% improvement of at least 3 of the above, and
• >30% worsening in no more than 1 of the above

Inclusion/Exclusion Criteria

• New onset poly JIA (RF-/+)
  – Within 12 months of disease onset
  – Ages 2-16 yrs
  – No active uveitis or history of uveitis
• Permitted prior meds other than NSAIDs
  – Steroids
    • 2 joint injections allowed
    • ≤ 4 weeks oral, must be off 1 week
  – MTX up to 6 weeks (<0.5 mg/kg/week)
  – No prior biologics or other DMARDs
• Negative PPD

Treatment Arms

Treatment Arm 1 (M-E-P)

• Weekly
  – MTX 0.5 mg/kg SQ (40 mg max)
  – Etanercept 0.8 mg/kg SQ (50 mg max)
• Daily
  – NSAID
  – Folate 1 mg
  – Prednisolone 0.5 mg/kg/d (60 mg max)
    (tapered to zero by 17 weeks)

Treatment Arm 2 (MTX)

• Weekly
  – MTX 0.5 mg/kg SQ
  – Placebo Etanercept SQ
• Daily
  – NSAID
  – Folate 1mg
  – Placebo Prednisolone
    (tapered to zero by 17 weeks)

TRial of Early Aggressive Treatment in JIA

Consented and Screened

Randomized

Blinded Treatment Arm 1 or 2

MONTH 4

ACR Pedi 70 achieved

Blinded Treatment Arm 1 or 2

MONTH 4

ACR Pedi 70 not achieved

Open: M-E-P

Treatment Arm 1: MTX + Etanercept + daily prednisolone (tapered to 0 by 17 wks)
Treatment Arm 2: MTX + placebo Etanercept + placebo prednisolone (tapered to 0 by 17 wks)
**Trial of Early Aggressive Treatment in JIA**

- **Consent and Screening**
- **Randomization**
- **Blinded Treatment Arm 1 or 2**
- **MONTH 6 CID achieved**
- **Blinded Treatment**
- **Blinded Treatment Arm 1 or 2**
- **MONTH 6 CID not achieved**
- **Open M-E-P**
- **End of Trial**

*Treatment Arm 1: MTX + Etanercept + daily prednisolone (tapered to 0 by 17 wks)*
*Treatment Arm 2: MTX + placebo Etanercept + placebo prednisolone (tapered to 0 by 17 wks)*

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### Baseline Characteristics

<table>
<thead>
<tr>
<th>Treatment</th>
<th>M-E-P (N=42)</th>
<th>MTX (N=43)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean mos of symptoms</td>
<td>4.9</td>
<td>5.2</td>
<td>NS</td>
</tr>
<tr>
<td>Mean MD global disease activity</td>
<td>7.0</td>
<td>7.1</td>
<td>NS</td>
</tr>
<tr>
<td>% RF +</td>
<td>33%</td>
<td>40%</td>
<td>NS</td>
</tr>
<tr>
<td>% Elevated ESR</td>
<td>48%</td>
<td>63%</td>
<td>NS</td>
</tr>
<tr>
<td>Mean # of active joints</td>
<td>18</td>
<td>26</td>
<td>0.018</td>
</tr>
<tr>
<td>Mean ESR mm/hr</td>
<td>29</td>
<td>45</td>
<td>0.017</td>
</tr>
</tbody>
</table>

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### 4 Months: ACR Pediatric 70 *

<table>
<thead>
<tr>
<th>Treatment</th>
<th>M-E-P</th>
<th>MTX</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACR Pedi 70 Achieved</td>
<td>30 (71%)</td>
<td>19 (44%)</td>
<td>49</td>
</tr>
<tr>
<td>ACR Pedi 70 not achieved</td>
<td>12 (29%)</td>
<td>24 (56%)</td>
<td>36</td>
</tr>
<tr>
<td>Totals</td>
<td>42</td>
<td>43</td>
<td>85</td>
</tr>
</tbody>
</table>

* P = 0.011

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### 6 Months: Clinical Inactive Disease *

<table>
<thead>
<tr>
<th>Treatment</th>
<th>M-E-P</th>
<th>MTX</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Inactive Disease Achieved</td>
<td>17 (40%)</td>
<td>10 (23%)</td>
<td>27 (32%)</td>
</tr>
<tr>
<td>Clinical Inactive Disease not Achieved</td>
<td>25 (60%)</td>
<td>33 (77%)</td>
<td>58 (88%)</td>
</tr>
<tr>
<td>Totals</td>
<td>42</td>
<td>43</td>
<td>85</td>
</tr>
</tbody>
</table>

* P = 0.088

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### 12 Months: Clinical Remission on Medications *

<table>
<thead>
<tr>
<th>Treatment</th>
<th>M-E-P</th>
<th>MTX</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRM</td>
<td>9 (21%)</td>
<td>3 (7%)</td>
<td>12 (14%)</td>
</tr>
<tr>
<td>No CRM</td>
<td>33 (79%)</td>
<td>40 (93%)</td>
<td>73 (86%)</td>
</tr>
<tr>
<td>Totals</td>
<td>42</td>
<td>43</td>
<td>85</td>
</tr>
</tbody>
</table>

*P = 0.053
Window of Opportunity - Importance of Early Therapy

The earlier after disease onset the patient started aggressive therapy, the greater the likelihood of attaining clinical inactive disease at 6 months.

<table>
<thead>
<tr>
<th>Number of months earlier that treatment was started after onset of disease</th>
<th>Odds ratio of achieving CID at 6 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 month</td>
<td>1.32</td>
</tr>
<tr>
<td>3 months</td>
<td>2.31</td>
</tr>
<tr>
<td>6 months</td>
<td>5.31</td>
</tr>
</tbody>
</table>

Median Percent Improvement from Baseline in ACR Pediatric Core Variables

<table>
<thead>
<tr>
<th></th>
<th>4 months</th>
<th>6 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of joints w/ LOM</td>
<td>88</td>
<td>98</td>
</tr>
<tr>
<td>MD global assm't</td>
<td>78</td>
<td>100</td>
</tr>
<tr>
<td>Overall well-being</td>
<td>69</td>
<td>83</td>
</tr>
<tr>
<td>C-HAQ</td>
<td>83</td>
<td>100</td>
</tr>
<tr>
<td>ESR</td>
<td>67</td>
<td>64</td>
</tr>
</tbody>
</table>

*P = NS; all other P values for improvement from baseline ≤ 0.001

Safety

No difference between treatment arms:

- Serious adverse events (n=3)*
- Adverse events grade 3 or higher (n=4)*
- Infections requiring systemic antibiotics (n=53, 96% oral)*

*All events resolved

Infections Requiring Systemic Therapy

- MTX
  19 episodes/ 247 months of therapy: 0.08/mo
- MTX + Etn
  16 episodes/ 297 months of therapy: 0.05/mo
- MTX + Etn + pred
  18 infections/ 360 months of therapy: 0.05/mo

Summary

- TREAT is unique and innovative as an investigator initiated clinical trial in poly JIA
- First Double Blind RCT in JIA to investigate:
  - Treatment of early onset patients
  - Two aggressive treatment arms
  - Clinical Inactive Disease as the primary outcome
  - Potential to set standards for treatment, timing of response, and outcome for poly JIA
- Data and samples represent a tremendous opportunity for additional clinical and translational investigations in poly JIA

Conclusions

- There was not a statistically significant difference in the proportion of subjects achieving CID at 6 months between the two aggressive treatment arms
- CID by 6 months of therapy and CRM by 12 months are achievable in a substantial proportion of patients with severe poly JIA
- Best chance to achieve this level of response is in patients that have aggressive treatment started earlier in their disease course
- M-E-P results in a more rapid and sustained response in a greater proportion of patients than MTX alone, although MTX SQ can be an effective treatment
Safety - Serious Adverse Events

• Psychosis
  - Open label MTX + Etn + pred
  - Pred tapered – resolved and patient completed study

• Pneumonia
  - Blinded MTX + Etn + pred - resolved

• Septic joint
  - Open label MTX + Etn + pred (but off meds for 2 months at time of event) - resolved

Safety
Adverse Events Grade 3 and higher*

• MTX
  - None

• MTX + Etn
  - Low WBC; adjustment reaction

• MTX + Etn + pred
  - Low WBC; peritonsillar abscess

*All events resolved
Ongoing Ancillary Studies

- **Jim Jarvis:**
  Systems and Dynamics in Polyarticular JIA

- **Sampath Prabhu:**
  Genomics of Childhood Onset Rheumatoid Arthritis

- **Sue Thompson:**
  Defining the complex genetics of Juvenile Idiopathic Arthritis by genotyping additional patient cohorts and including TREAT samples for integrative analysis

- **Salvo Albani/Nora Singer:**
  Mechanisms of Immune Modulation in JIA

- **Nora Singer/Sarah Ringold:**
  Metrics and Biomarkers in JIA

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**Clinical Trial of Early Aggressive Treatment in JIA**

- **Consent and Screening**
- **Randomization**
  - **Blinded Treatment Arm 1 or 2**
  - **Open M-E-P**
- **MONTH 4**
  - ACR Pedi 70 not achieved
- **MONTH 5**
  - CID not achieved
- **MONTH 6**
  - CID achieved
  - Blinded Treatment
- **End of Trial**

**Treatment Arm 1:** MTX + Etanercept + daily prednisolone (tapered to 0 by 17 wks)

**Treatment Arm 2:** MTX + placebo Etanercept + placebo prednisolone (tapered to 0 by 17 wks)