Juvenile Idiopathic Arthritis Treatment

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Evidence


Timelines of JIA treatment development


Response to treatment measures

ACR- Pedi 30 defines a minimum response:

≥ 30% improvement in 3 of 6 core set variables no more than 1 variable worsening ≥ 30%.

Oligoarticular Juvenile Idiopathic Arthritis

ANA + association HLA B1, B8
Uveitis Risk
Joint steroid injection

• NSAIDs
  (Symptomatic treatment)
Pain relief

• Naproxen
• Diclofenac

Polyarticular Juvenile Idiopathic Arthritis

Positive Rheumatoid Factor – Negative Rheumatoid Factor
Positive ANA – Negative ANA
Proliferative Symetric Synovitis

J Jacobs, 1993
# METHOTREXATE

<table>
<thead>
<tr>
<th>Dosage</th>
<th>Oral, SC or IM</th>
<th>Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 -15 mg/m²/wk oral or parenteral (IM or SC)</td>
<td>Oral – up to 15 mg Parenteral (SC or IM) doses &gt;15 mg</td>
<td>Mild: Oral Ulcers, Alopecia Gastritis Transaminase increase</td>
</tr>
<tr>
<td>Response 3-6 months</td>
<td>Folic Acid (Folinic) 1mg/day 5-6 times/wk</td>
<td>Severe: Cytopenia Liver toxicity Interstitial pneumonia</td>
</tr>
<tr>
<td>30-40% Response Failure</td>
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</tbody>
</table>

Methotrexate Dose-Response

• **Oral MTX**
  Double-blind trial of 5 mg/m$^2$/wk and 10 mg/m$^2$/wk versus PLACEBO

• **SC or IM MTX**
  Controlled dose-response trial comparing oral MTX and parenteral MTX (SC or IM) escalating in a double-blind comparison of high and intermediate doses
  Efficacy was reached with 15 mg/m$^2$/wk (Maximum 20 mg/wk)

• **LEFLUNOMIDE or MTX**
  “Double-dummy” trial (blind) comparing Leflunomide or Metotrexate during 16 weeks and 32 weeks blind extension.
  ACR Pedi 30 response to both, but MTX efficacy was higher than leflunomide
Growth Impact

Methotrexate response in 60-70%
POZNANSKI INDEX

The measure of proportional relationship of the length of the second metacarpal bone correlates with height and linear bone growth: a good measure of arthritis progression.

In the first year of treatment with METHOTREXATE this index is a good predictor of function and limitation due to Polyarticular JIA.

Methotrexate safety and long term outcome

• Safety and Adverse Events Monitoring
  Gastro-intestinal adverse events, liver toxicity and folate supplementation.

• Magnitude of response and long term outcome

• Time of treatment onset: Early treatment results in better outcome

• Timing withdrawal when JIA attains clinical remission

• Biomarkers and outcome predictors
Anti-TNF Treatment: Mechanism of Action

ETANERCEPT the first biologic agent tested in a withdrawal design

INFLIXIMAB and METHOTREXATE versus PLACEBO in POLYARTICULAR JIA

Adalimumab and Methotrexate Efficacy

Abatacept Efficacy
T-cell receptor blockage

Enthesitis Related Arthritis

Anklosing Spondylitis

Reactive Arthritis

Inflammatory Bowel Disease related arthritis

Psoriatic Arthritis

Anterior Uveitis

HLA-B27

Undifferentiated Arthritis

... A rose by any other name is still a rose... WS

Enthesitis Related Arthritis Treatment

Enthesitis and Spine Involvement

Burgos-Vargas R, Clark P Axial involvement in the seronegative enthesopathy and arthropathy syndrome and it is progress to ankylosing spondylitis. J Rheumatol 1989, 16: 192-197

USTEKINUMAB –IL-23 blockage experimental evidence / “TOPAS” trial Anti IL12/23
Psoriatic Arthritis

* CLIPPER study: First trial with anti-TNF for extended oligoarticular, psoriatic and enthesitis related arthritis
Uveitis Treatment
Refactory Uveitis Treatment

- Prednisolone (topic plus midriatics)
- Prednisolone (oral) short course*
- Methotrexate
  

- Etanercept
  
  Reiff A Arthritis Rheum 2003, 48: 2079-80

- Infliximab and Adalimumab
  
  Sukumaran S et al. ISRN Rheumatology 2012: 765380

- Abatacept
  

- Tocilizumab
  
  NCT 01603355 e NCT 01717170

- Micofenilato Mofetil
  

- Rituximab
  
## Practical Guidelines and Recommendations

<table>
<thead>
<tr>
<th></th>
<th>Australia</th>
<th>Germany</th>
<th>UK and Ireland</th>
<th>United States</th>
<th>United States</th>
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<tbody>
<tr>
<td>LITERATURE</td>
<td>2000-2007</td>
<td>up to 2010</td>
<td>-</td>
<td>1966-2009</td>
<td>up to 2013</td>
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<tr>
<td>METHOD</td>
<td>Literature review e-mail circulation</td>
<td>Systematic review Delphy and Nominal consensus techniques</td>
<td>Informal Consensus</td>
<td>Systematic Review RAND/UCLA model Task force/Expert Pannel</td>
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<tr>
<td>TARGET</td>
<td>Primary care</td>
<td>Pediatric Rheumatol</td>
<td>Generalist</td>
<td>Pediatric Rheumatol</td>
<td>Pediatric Rheumatol</td>
</tr>
</tbody>
</table>

## DMARDS – Disease modifying agents

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dose</th>
<th>It can not be used</th>
<th>Adverse Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>METHOTREXATE</td>
<td>10-15 mg/m²/WK oral, SC (max 25 mg/m²)</td>
<td>Liver dysfunction, renal, dyserithropoiesis, active infection, pregnancy and lactancy</td>
<td>Nausea, vomits, anorexia, transaminase increase, myelodysplasia theratogenesis</td>
</tr>
<tr>
<td>SULFASALAZINE</td>
<td>50mg/Kg/day 2-3 daily doses (max 2g/day)</td>
<td>Allergy, salicylates, sulphas, Systemic JIA</td>
<td>Allergic reactions , GI intolerance, myelodysplasia</td>
</tr>
<tr>
<td>LEFLUNOMIDE</td>
<td>• &lt;20Kg: 100mg 1 day/10 mg alt days</td>
<td>Immunodeficiency, dyserythropoiesis, active infection, liver failure, low albumin, pregnancy and lactancy</td>
<td>GI symptoms, allergic reactions, high transaminases, abnormal blood cell count , theratogenesis</td>
</tr>
<tr>
<td></td>
<td>• 20-40 Kg: 200 mg 2 days 10mg/day</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• &gt;40 Kg: 100 mg 3 days 20 mg/day</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CYCLOSPORIN</td>
<td>3-7 mg/Kg/day oral or IV</td>
<td>Renal Failure, Hipertension, Infection</td>
<td>Hypertension, Renal Toxicity, Ca and Mg depletion, cramps, hyrsutism, gum hypertrophy, PRES encephalopathy</td>
</tr>
</tbody>
</table>

Prince FHM et al. BMJ 2010 dx.doi.org/10.1136/bmj.c6434 03 dec 2010
<table>
<thead>
<tr>
<th>Agent</th>
<th>Action</th>
<th>Dosis</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>ETANERCEPT*</td>
<td>TNF alpha receptor fusion protein</td>
<td>0,4 mg/Kg 2 times /wk 0,8 mg/Kg/wk SC SC max 50 mg/wk</td>
<td>Polyarticular JIA Extended Oligo JIA Rarely Persistent Oligo JIA Plaque Psoriasis</td>
</tr>
<tr>
<td>ADALIMUMAB*</td>
<td>Human Monoclonal antibody to TNF</td>
<td>&lt;30 Kg 20 mg / 2 wk &gt;30 Kg 40 mg/ 2 wk SC</td>
<td>Polyarticular Course JIA Crohn’s Disease Ulcerative Colitis</td>
</tr>
<tr>
<td>INFliximab</td>
<td>Chimeric (rat/human) Monoclonal antibody to human TNF</td>
<td>6-10 mg/Kg IV 0,2 and 6 wks, every 4-8 wks</td>
<td>Rheumatoid Arthritis Crohn’s Disease Ulcerative Colitis Plaque Psoriasis UVEITIS</td>
</tr>
<tr>
<td>GOLIMUMAB</td>
<td>Human Monoclonal antibody to TNF</td>
<td>Pediatric doses not yet identified (50 mg every 4 wks) SC NCT 01230827</td>
<td>Rheumatoid Arthritis Psoriatic Arthritis Ankylosing Spondylitis</td>
</tr>
<tr>
<td>CERTOLIZUMAB-PEGOL</td>
<td>Human Monoclonal antibody to TNF Fab - PEG</td>
<td>Pediatric doses not yet identified RA 400 mg 0,2,4 wk, 200 mg/2 wk or 400mg/4 wks SC NCT 01550003</td>
<td>Rheumatoid Arthritis</td>
</tr>
</tbody>
</table>

Anti-TNF Risks of Adverse Events

- Latent tuberculosis reactivation, other opportunistic infections
- Demyelinating diseases: onset or exacerbation of previous disease
- Auto-antibodies development (ANA, anti-DNA, a-CL)
- Autoimmune phenomena and autoimmune diseases (lupus-like)
- Infusion and post-infusion reaction (Infliximab)
- Heart Failure worsening
- Malignancy increased incidence

REQUIRES LONG-TERM PHARMACOVIGILANCE
Systemic Arthritis

High spiking fever

Evanescent rash

- WBC count and neutrophils
- Platelets
- Microcytic anemia
- High ESR and CRP
- High levels of Ferritin

Serositis

Amyloidosis
Systemic Glucocorticoids

Prednisone- Prednisolone- Methyl-prednisolone

- Fever, Pericarditis, Myocarditis
- Macrophage activation syndrome
- ‘Bridge’ for DMARD

Systemic Juvenile idiopathic Arthritis

Macrophage Activation Syndrome (MAS)

REACTIVE HEMOPHAGOCYTIC LYMPHOHYSTIOCITOSIS

- Cytopenia
- Transaminase increase
- Decreased fibrinogen
- Coagulopathy
- Decreased ESR
- Very high ferritin levels
- Hyponatremia
- Hypoalbuminemia
- Hemophagocytosis

Response to high dose glucocorticoids
Cyclosporin A

IL-1 Receptor signaling block


Response to Canakinumumab

Pathogenic role of IL-6 in Systemic JIA

SERUM AND SYNOVIAL FLUID


CHRONIC ANEMIA


GROWTH AND DEVELOPMENT

Anti-IL-6 treatment of Systemic JIA

TOCILIZUMAB IN SYSTEMIC JUVENILE IDIOPATHIC ARTHRITIS

Growth and development after anti-IL6 treatment

## Biologic treatment: anti-IL-1, anti-IL-6

<table>
<thead>
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<th>Agent</th>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>ANAKINRA</strong></td>
<td>IL-1 receptor antagonist</td>
<td>1-2 mg/Kg/day SC Max 100 mg</td>
<td>Cryopirin periodic fevers</td>
</tr>
<tr>
<td><strong>RILONACEPT</strong></td>
<td>IL-1 receptor fusion protein antibody (IL 1RacP-FC)</td>
<td>initial Dosis 4.4 mg/wk (max 320 mg) SC Maintenance 2.2 mg/wk (max 160 mg) SC</td>
<td>Cryopirin periodic fevers</td>
</tr>
<tr>
<td><strong>CANA KIMUMAB</strong></td>
<td>Humanized human anti IL-1 beta antibody</td>
<td>4 mg/Kg/dosis Max 300 mg/4 wk SC</td>
<td>Cryopirin periodic fevers</td>
</tr>
<tr>
<td><strong>TOCILIZUMAB</strong></td>
<td>Humanized human anti IL-6 antibody</td>
<td>&lt; 30 Kg 12 mg/Kg every 2 wk &gt; 30 Kg 8 mg/Kg every 4 wk Max 300 mg IV (SC preparation is in development)</td>
<td>Systemic JIA CLINICAL TRIAL Macrophage activation syndrome</td>
</tr>
</tbody>
</table>

**Biologic treatment– T cell selective block and B-cell depletion**

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<th>Agent</th>
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</tr>
</thead>
<tbody>
<tr>
<td>ABATACEPT</td>
<td>co-stimulatory blockage 80/86 (CTLA4 Ag)</td>
<td>10 mg/Kg 0, 2, 4 and every 4 weeks (max 1000 mg)</td>
<td>Polyarticular Course JIA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IV SC in development NCT 01844518</td>
<td></td>
</tr>
<tr>
<td>RITUXIMAB</td>
<td>Chimeric monoclonal anti-CD 20 antibody</td>
<td>750 mg/m2/dosis (max 1000 mg) 2 doses in 2 weeks time</td>
<td>Non Hodgkin B-Cell Lymphoma Systemic Lupus Erythematosus Systemic JIA ** (no trial)</td>
</tr>
</tbody>
</table>

The armamentarium of anti-rheumatic drugs available for the treatment of JIA

Hinze, C. et al. (2014) Management of juvenile idiopathic arthritis: hitting the target
*Nat. Rev. Rheumatol.* doi:10.1038/nrrheum.2014.212
Thank you for early treatment

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