Adult-onset Still’s disease – a polygenic autoinflammatory disease

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IL-1 mediated diseases – past present and future
Såstaholm Conference Center 8 October 2011
A proposed classification of the immunological diseases

**AUTOINFLAMMATORY**

- **RARE MONOGENIC AUTOINFLAMMATORY DISEASES**
  - FMF, TRAPS, HIDS, PAPA
  - Blau syndrome (uveitis)

- **POLYGENIC AUTOINFLAMMATORY DISEASES**
  - Crohn disease, ulcerative colitis
  - Degenerative diseases, e.g., osteoarthritis
  - Gout/pseudogout/other crystal arthropathies
  - Some categories of reactive arthritis and Psoriasis/psoriatic arthritis (no MHC associations)
  - Self-limiting inflammatory arthritis including diseases clinically presenting as RA
  - Storage diseases/ congenital diseases with associated tissue inflammation
  - Non-antibody associated vasculitis including giant cell and Takayasu arteritis
  - Idiopathic uveitis
  - Acne and acneform associated diseases
  - Some neurological diseases, e.g., acute disseminated encephalomyelitis
  - Erythema nodosum associated disease, including sarcoidosis

**MIXED PATTERN DISEASES**

- with evidence of acquired component (MHC class I associations) and autoinflammatory components

- **CLASSIC POLYGENIC AUTOIMMUNE DISEASES**
  - Ankylosing spondylitis
  - Reactive arthritis
  - Psoriasis/psoriatic arthritis
  - Behcet Syndrome
  - Uveitis (HLA-B27 associated)

- Rheumatoid arthritis
- Autoimmune uveitis (sympathetic ophthalmaia)
- Coeliac disease
- Primary biliary cirrhosis
- Autoimmune gastritis/pernicious anaemia
- Autoimmune thyroid disease
- Addison disease
- Pemphigus, pemphigoid, vitiligo
- Myasthenia gravis
- Dermatomyositis, polymyositis, scleroderma
- Goodpasture syndrome
- ANCA associated vasculitis
- Type 1 diabetes
- Sjögren syndrome
- Systemic lupus erythematosus

**AUTOIMMUNE**

- **RARE MONOGENIC AUTOIMMUNE DISEASES**
  - ALPS, IPEX, APECED

Contents

- Adult-onset Still’s disease (AOSD) – general description including therapeutic strategies
- Open, randomised multicentre study of anakinra in corticosteroid-dependent, refractory AOSD
Adult-onset Still’s disease*

- **Cardinal features**
  - Spiking fever
  - Evanescent salmon-pink maculopapular rash
  - Arthritis
  - Neutrophilic leukocytosis
- **Other features**
  - Sore throat/pharyngitis
  - Myalgia
  - Lymph node or spleen enlargement
  - Pleuritis or pericarditis
  - Elevated levels of liver enzymes
  - Abdominal pain
  - High serum ferritin

*Described by Eric Bywaters in 1971*
Biological features of AOSD

- Marked leukocytosis and neutrophilia
- Leukopenia and thrombocytopenia signify macrophage activation syndrome (MAS)
- Vigorous acute phase reaction (often CRP > 100 mg/l and ESR > 100 mm/h). Potential risk of AA amyloidosis.
- Hepatitis, potentially serious
- Polyclonal hypergammaglobulinemia but no signs of autoimmunity, such as RF, ANA, anti-CCP
- Marked hyperferritinemia, low glycosylated fraction
- Coagulation abnormalities in MAS
AOSD- Epidemiology

- Occurs worldwide
- Incidence: about 5/million/year
- Disease onset usually between 16 and 35 years of age
- May also affect elderly people
- No specific familial aggregation
Etiology and pathogenesis

- Immunological pathways
  - Reactive hyperplasia in lymph nodes: Macrophages, neutrophils, B-lymphocytes and plasma cells, T-lymphocytes
  - High levels of IL-1beta, IL-6, IL-18, TNF-alpha and IFN-gamma
  - Association between serum IL-6 and IL-18 levels and systemic symptoms

- Genetic background
  - Association with HLA-Bw35 allele and some HLA-DRB1 subtypes.
  - Inconclusive data

- Environmental factors
  - Several viruses, bacteria and parasites related to AOSD onset and recurrence
Pathogenesis of AOSD – ”a bag of cytokines”

Fautrel B.
Best Pract Res Clin Rheumatol
Differential diagnosis

- "AOSD is a painstakingly difficult diagnosis" (J. Cush)
- **A diagnosis of exclusion:**
- Infections
  - Septicemia, infectious endocarditis, tuberculosis, viral hepatitis etc.
- Malignant neoplastic diseases
  - Hodgkin lymphoma, non-Hodgkin lymphoma, solid cancers, myeloproliferative disorders, paraneoplastic syndromes etc.
- Systemic diseases
  - Vasculitides, reactive arthritis, myositis, SLE, rheumatoid arthritis, sarcoidosis, hereditary autoinflammatory diseases/syndromes, sarcoidosis, drug-related hypersensitivity etc.

- Classification criteria: Yamaguchi; Cush; Fautrel
Natural history of AOSD

- Systemic, self-limited monocyclic evolution in 19-44%
  - Single flare and complete remission in weeks or months
- Intermittent or polycyclic pattern in 10-41%
  - Recurrence of systemic or articular flares separated by periods of remission
- Chronic evolution in 35-67%
  - 1/3 develop erosive arthritis
Therapeutic strategies in AOSD

- Based on observational studies
- First-line
  - NSAID can control symptoms in a small minority of cases
  - Corticosteroids usually required. Usually dramatic response but dependence on corticosteroids common
- Second-line
  - Methotrexate can control disease activity and allows for steroid dose sparing
  - Azathioprine, leflunomide, cyclosporin A, gold salts
- Third-line
  - IL-1 blockade (anakinra), TNF blockade (infliximab, etanercept, adalimumab), IL-6 blockade (tocilizumab), B-cell depletion (rituximab)
Therapeutic strategies in AOSD

The basis of treatment with cytokine inhibitors in AOSD

Rapid Responses to Anakinra in Patients With Refractory Adult-Onset Still’s Disease

Avril A. Fitzgerald,¹ Sharon A. LeClercq,² Alexander Yan,² Joanne E. Homik,³ and Charles A. Dinarello⁴

![Graph showing temperature over days with data points and a table listing changes in various biomarkers.]

<table>
<thead>
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<th>Biomarker</th>
<th>Pre-treatment</th>
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<td>IL-1Ra</td>
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<td>IL-6</td>
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<td>IL-18</td>
<td>2558; 2238</td>
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<td>Ferritin</td>
<td>422 8,400 543</td>
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<td>573 170</td>
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<td>CRP</td>
<td>47 116</td>
<td></td>
<td>86 9.6</td>
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<td>Hgb</td>
<td>11.3 10.2</td>
<td></td>
<td>10.7 11.6</td>
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<tr>
<td>WBC</td>
<td>8,300 (73%)</td>
<td>14,400 (84%)</td>
<td>14,600 (86%) 5,700 (68%)</td>
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<td>Prednisone (30, 25)</td>
<td>(20)</td>
<td>(20)</td>
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<td>MTX (15)</td>
<td>(25)</td>
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Dec 16/02
5 weeks

Arthritis Rheum 2005;52:1794-1803
Anakinra in SoJIA and AOSD

- A retrospective study of 35 patients
  - 20 with SoJIA, 15 with AOSD
  - Anakinra 1-2 mg/kg/day for children and 100 mg/day for adults
  - All except 1 had active arthritis
- 5/20 of SoJIA patients and 11/15 of AOSD patients had at least a 50% ACR response.
- Complete response: 4/20 in SoJIA group and 9/15 in AOSD group
- Enabled reduction or termination of cortisone in 10/20 (SoJIA) and 14/15 (AOSD)
- Anakinra was stopped in 4, 2 with a cutaneous reaction and 2 with an infection

The ANAJIS trial

- A multicentre randomised double-blind placebo-controlled trial to assess the efficacy of anakinra in SoJIA
- Duration: One month
- Two groups, 12 in each
- After 1 month 8 responders used anakinra and 1 responder placebo
- At 1 month 10 patients from the placebo group switched to anakinra.
- Conclusion: Anakinra is effective in SoJIA, at least in the short term.

Open, randomized study where the IL-1 antagonist anakinra was compared with traditional treatment with one disease-modifying antirheumatic drug in refractory AOSD.

A Nordic study: All 5 university hospitals and 2 regional hospital in Finland and several university hospitals in Sweden, Norway and Denmark participated.


Duration: 24 weeks followed by an open phase up to one year.

Principal investigator: Dan Nordström, Helsinki.
Objectives for AOSD05

- To monitor disease activity and symptoms in patients receiving anakinra, compared to those of a traditional DMARDs (methotrexate, azathioprine, leflunomide, or cyclosporin A) in patients with corticosteroid-dependent, refractory AOSD.

- Refractory disease was defined as a state where treatment with a corticosteroid (prednisolone equivalent $\geq 10$ mg/day for 2 months and NSAID) did not control the signs and symptoms of the disease.
Endpoints

Primary endpoint:
- Number of patients reaching remission after 8 weeks of treatment
  - Remission stated as afebrile [≤37°C of body temperature]; acute phase reactants [C-reactive protein and/or ferritin] within normal limits and normal swollen or tender joint counts (SJC/TJC)

Secondary endpoints:
- Number of patients reaching remission at two consecutive study visits during the whole treatment period of 24 weeks
- Reduction of values of BT, CRP and ferritin; Reduction of corticosteroid dosage; Improvement of Global/Disease Activity VAS, HAQ, SF-36.
- Number of patient withdrawals due to adverse events or lack of efficacy
Anakinra + corticosteroid

MTX, methotrexate; AZA, azathioprine; LEF, leflunomide; CyA, cyclosporin A; SSZ, sulphasalazine
<table>
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<th>PATIENT N:o</th>
<th>CITY</th>
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### Patients at baseline

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<tr>
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<th>DMARD N=10</th>
<th>ANAKINRA N=12</th>
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<tr>
<td>Women/men</td>
<td>5 / 5</td>
<td>6 / 6</td>
</tr>
<tr>
<td>Drug</td>
<td>MTX 6, AZA 3, LEF 1</td>
<td>anakinra 100 mg/day</td>
</tr>
<tr>
<td>Age, mean (SD)</td>
<td>39 (17)</td>
<td>39 (18)</td>
</tr>
<tr>
<td>CRP, mg/l, mean (range)</td>
<td>25 (0.2-116)</td>
<td>25 (0.5-104)</td>
</tr>
<tr>
<td>Ferritin, μg/l, mean (range)</td>
<td>186 (17-680)</td>
<td>354 (18-1740)*</td>
</tr>
<tr>
<td>ESR, mm/h, mean (range)</td>
<td>17 (1-37)</td>
<td>24 (5-84)</td>
</tr>
<tr>
<td>Doctor’s global, mm, mean</td>
<td>21 (2-43)</td>
<td>21 (6-45)</td>
</tr>
<tr>
<td>Patient’s global, mm, mean</td>
<td>28 (0-65)</td>
<td>25 (3-60)</td>
</tr>
<tr>
<td>Swollen/tender joints</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>Fever</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Prednisolone, mean (range)</td>
<td>18.5 mg (10-25)</td>
<td>22.5 mg (10-60)*</td>
</tr>
</tbody>
</table>
Comparison between groups

- Patient groups (anakinra vs. DMARD) were similar except for
  - Baseline ferritin levels (354 μg/l, range 18-1740 vs. 186 μg/l, range 17-680)
  - Baseline prednisolone dose (22.5 mg, range 10-60 vs. 18.5 mg, range 10-25).
Results

- Remission rates at week 24
  - Anakinra group: 6/12
  - DMARD group: 2/10
- In both groups the prednisolone doses could be reduced significantly, by (mean) 10.8 and 10.5 mg, respectively.
- 4 patients experienced worsening of AOSD: 2 on anakinra in OLE phase and 2 on DMARD within 24 weeks.
- 5 patients on DMARD withdrew before week 24 because of lack of efficacy, p=0.0014.
Patients in remission

- Week 4: 3 on DMARD vs. 6 on anakinra
- Week 8: 5 on DMARD vs. 7 on anakinra
- Week 24: 2 on DMARD vs. 6 on anakinra
Longitudinal monitoring of CRP

- Anakinra
- DMARD

$p=0.75$
Prednisolone dosage

![Graph showing prednisolone dosage over time for Anakinra and DMARD treatments.]

- Anakinra
- DMARD

$p=0.80$
Physical and mental health indices

- **SF-36 / Physical Health Summary:**
  - p = 0.011
  - Anakinra vs. DMARD

- **SF-36 / Mental Health Summary:**
  - p = 0.74
  - Anakinra vs. DMARD
Conclusions

- A randomized 24-week study which shows that remission can be achieved with DMARDs or with anakinra in refractory AOSD.
- Better physical well being among anakinra users (SF-36).
- No severe adverse events
- Treatment failures only among DMARD users (N=5).
- Significant decrease in corticosteroid dose in both groups.
"Du blir aldrig färdig och det är som det ska"
"You will never be ready and that is as it should be."

Tomas Tranströmer, Nobel laureate 2011
Yamaguchi’s diagnostic criteria for AOSD

Major criteria
- Fever > 39°C, lasting > 1 week
- Arthralgias lasting > 2 weeks
- Typical rash
- WBC > 10, granulocytes > 80%

Minor criteria
- Sore throat
- Lymphadenopathy and/or splenomegaly
- Liver dysfunction
- Negative RF and ANA

Diagnosis of AOSD: 5 or more criteria including 2 or more major criteria and exclusion of other major disease entities
Cush’s diagnostic criteria for AOSD

**Major (2 points)**
- Quotidian fever >39°C
- Evanescent rash
- WBC>12.0 + ESR>40
- Negative RF and ANA
- Carpal ankylosis

**Minor (1 point)**
- Onset age <35 years
- Arthritis
- Prodromal sore throat
- RES involvement or lymphadenopathy
- Serositis
- Cervical or tarsal ankylosis

Probable AOSD: 10 points with 12 weeks observation
Definite AOSD: 10 points with 6 months observation
SoJIA and AoSD patients’ response to anakinra in an intention-to-treat analysis at 3 and 6 months.

Changes over time of the daily prednisone dose in patients that responded to anakinra.