UPDATES IN RHEUMATOLOGY 2018

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Clinical Assistant Professor, UIUC
Course Director Musculoskeletal, CICOM

November 10, 2018
Disclosures

• I have no financial disclosures.

• I and my spouse have no relationships with any entity producing, marketing, rescheduling or distribute ink healthcare goods or services consumed by, or used on, patients.

• I will discuss off label use of certain products.
ACR/ARA 1987 Criteria for Diagnosis of Rheumatoid Arthritis

- Four or more of the following criteria must be present:
  - Morning stiffness > 1 hour
  - Arthritis of ≥ 3 joint areas
  - Arthritis of hand joints (MCPs, PIPs, wrists)
  - Symmetric swelling (arthritis)
  - Serum rheumatoid factor
  - Rheumatoid nodules
  - Radiographic changes

- First four criteria must be present for 6 weeks or more
## 2010 ACR/EULAR Classification Criteria for RA

### Joint Distribution (0-5)

<table>
<thead>
<tr>
<th>1 large joint</th>
<th>0</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-10 large joints</td>
<td>1</td>
</tr>
<tr>
<td>1-3 small joints</td>
<td>2</td>
</tr>
<tr>
<td>4-10 small joints</td>
<td>3</td>
</tr>
<tr>
<td>&gt;10 joints (at least one small joint)</td>
<td>5</td>
</tr>
</tbody>
</table>

### Serology (0-3)

| Negative RF AND negative ACPA | 0 |
| Low positive RF OR low positive ACPA | 2 |
| High positive RF OR high positive ACPA | 3 |

### Symptom Duration (0-1)

<table>
<thead>
<tr>
<th>&lt;6 weeks</th>
<th>0</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥6 weeks</td>
<td>1</td>
</tr>
</tbody>
</table>

### Acute Phase Reactants (0-1)

| Normal CRP AND normal ESR | 0 |
| Abnormal CRP OR abnormal ESR | 1 |

≥6 = definite RA

What if the score is <6?

Patient might fulfill the criteria…

→ **Prospectively** over time (cumulatively)

→ **Retrospectively** if data on all four domains have been adequately recorded in the past
Antibodies against Cyclic Citrullinated Peptide (anti-CCP)

• Sensitivity is comparable to RF (50-75%)
• High Specificity (>95%) for RA, (Present in 70% of RA patients vs <5% of controls)
• Predictive of development of RA in undifferentiated arthritis
• May be detected in healthy individuals years before onset of clinical RA
• Marker of erosive disease
RADx5

• 14-3-3η Protein
• Anti-CEP-1 Ab IgG
• Anti-Sa Ab IgG
• Rheumatoid Factor IgM
• Anti-CCP Ab IgG/IgA
RADx5

• Diagnostic and prognostic panel for rheumatoid arthritis
• 3 novel markers (14-3-3\(\eta\), anti-CEP-1 and anti-Sa)
• 2 traditional markers (anti-CCP and RF-IgM)
• Enhance the diagnosis of RA in early or established disease
• Help predict disease severity
• In pre-clinical RA, positivity of anti-CEP-1 along with anti-CCP antibodies significantly raises the risk of imminently developing clinical RA
• If 14-3-3\(\eta\) and/or anti-Sa positivity is present, the disappearance or decrease of these antibodies with treatment is associated with less radiographic progression
14-3-3η

- 14-3-3η is an isoform of a family of proteins involved in the regulation of biologic activity of intracellular proteins. The 14-3-3η protein is released into the blood during synovial inflammation and is associated with the upregulation of factors leading to joint damage.

- It can be useful in helping make a diagnosis in both early and established RA, in identifying RA patients seronegative for anti-CCP and RF, and for monitoring clinical response to treatment as well as the risk of radiographic progression.

- It has also been found to be predictive of erosive disease in Psoriatic Arthritis patients (PsA).
Anti-CEP-1

• Antibodies to Citrullinated α-Enolase Peptide 1 (CEP-1):
  • Predict onset of symptoms in pre-clinical rheumatoid arthritis (RA)
  • Confirm the diagnosis of RA
  • Provide insight into the potential pathogenic triggers of RA.
Anti-Sa IgG

- Anti-Citrullinated Vimentin (Sa) antibodies:
  - Highly specific for RA
  - Found in early polyarthritis
  - Can identify patients that are anti-CCP and IgM-RF antibody negative
  - Predict more aggressive RA disease course
  - Disappearance of anti-Sa IgG antibodies 3 months after initiation of treatment is associated with less radiographic progression
Disease activity measure Scale

- Patient-driven composite tools
  - PAS
  - PAS-II
  - RAPID-3
- Patient and provider composite tool
  - CDAI
- Patient, provider, and laboratory composite tools
  - DAS28 (ESR or CRP)
  - SDAI
DAS 28-CRP Calculator / DAS-28 ESR Calculator

https://www.rheumatology.org/Portals/0/Files/DAS28%20CRP%20Calculator.xls

<table>
<thead>
<tr>
<th>Clinical Variable</th>
<th>Value</th>
<th>Tool</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tender Joint Count (0-28)</td>
<td>0</td>
<td>DAS28-CRP</td>
<td>0.96</td>
</tr>
<tr>
<td>Swollen Joint Count (0-28)</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRP (mg/L)</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient Global Activity (0-100 mm)</td>
<td>0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

https://www.rheumatology.org/Portals/0/Files/DAS28%20ESR%20Calculator.xls

<table>
<thead>
<tr>
<th>Clinical Variable</th>
<th>Value</th>
<th>Tool</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tender Joint Count (0-28)</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Swollen Joint Count (0-28)</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ESR (mm/hr)</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient Global Activity (0-100 mm)</td>
<td>0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Tool</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>DAS28-ESR</td>
<td>0.00</td>
</tr>
</tbody>
</table>

Disease Activity Range

<table>
<thead>
<tr>
<th>Remission</th>
<th>Low</th>
<th>Moderate</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 2.6</td>
<td>≥ 2.6 - &lt; 3.2</td>
<td>≥ 3.2 - ≤ 5.1</td>
<td>&gt; 5.1</td>
</tr>
</tbody>
</table>
# CDAI Calculator / SDAI Calculator

[https://www.rheumatology.org/Portals/0/Files/CDAI%20Calculator.xls](https://www.rheumatology.org/Portals/0/Files/CDAI%20Calculator.xls)

<table>
<thead>
<tr>
<th>Clinical Variable</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tender Joint Count (0-28)</td>
<td>0</td>
</tr>
<tr>
<td>Swollen Joint Count (0-28)</td>
<td>0</td>
</tr>
<tr>
<td>Patient Global Activity (0-10.0 cm)</td>
<td>0</td>
</tr>
<tr>
<td>Provider Global Activity (0-10.0 cm)</td>
<td>0</td>
</tr>
</tbody>
</table>

**Tool**

**Result**

**CDAI**

0.0

---

[https://www.rheumatology.org/Portals/0/Files/SDAI%20Calculator.xls](https://www.rheumatology.org/Portals/0/Files/SDAI%20Calculator.xls)

<table>
<thead>
<tr>
<th>Clinical Variable</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tender Joint Count (0-28)</td>
<td>0</td>
</tr>
<tr>
<td>Swollen Joint Count (0-28)</td>
<td>0</td>
</tr>
<tr>
<td>CRP (mg/dL)</td>
<td>0.1</td>
</tr>
<tr>
<td>Patient Global Activity (0-10.0 cm)</td>
<td>0</td>
</tr>
<tr>
<td>Provider Global Activity (0-10.0 cm)</td>
<td>0</td>
</tr>
</tbody>
</table>

**Tool**

**Result**

**Disease Activity**

<table>
<thead>
<tr>
<th>Range</th>
<th>Remission</th>
<th>Low</th>
<th>Moderate</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-76</td>
<td>≤ 2.8</td>
<td>&gt; 2.8 - 10.0</td>
<td>&gt; 10.0 - 22.0</td>
<td>&gt; 22.0</td>
</tr>
</tbody>
</table>

**Disease Activity**

<table>
<thead>
<tr>
<th>Range</th>
<th>Remission</th>
<th>Low</th>
<th>Moderate</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-86</td>
<td>0.0 - 3.3</td>
<td>3.4 - 11.0</td>
<td>11.1 - 26.0</td>
<td>26.1 - 86.0</td>
</tr>
</tbody>
</table>
# RAPID 3 Calculator

![Image of RAPID 3 Calculator](https://www.rheumatology.org/Portals/0/Files/RAPID%203%20Calculator.xls)

## Clinical Variable

<table>
<thead>
<tr>
<th>Clinical Variable</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient Global Activity (0-10.0 cm)</td>
<td>0</td>
</tr>
<tr>
<td>Patient Pain (0-10 cm)</td>
<td>0</td>
</tr>
<tr>
<td>Mean MDHAQ (0-3)</td>
<td>0</td>
</tr>
</tbody>
</table>

## Tool

<table>
<thead>
<tr>
<th>Tool</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>RAPID3</td>
<td>0.00</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Disease Activity</th>
<th>Remission</th>
<th>Low</th>
<th>Moderate</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>Range</td>
<td>0 - 1.0</td>
<td>&gt; 1.0 - 2.0</td>
<td>&gt; 2.0 - 4.0</td>
<td>&gt; 4.0 - 10</td>
</tr>
</tbody>
</table>
### PAS Calculator / PAS II Calculator

- [https://www.rheumatology.org/Portals/0/Files/PAS%20II%20Calculator.xls](https://www.rheumatology.org/Portals/0/Files/PAS%20II%20Calculator.xls)

<table>
<thead>
<tr>
<th>Clinical Variable</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient Global Activity (0-10.0 cm)</td>
<td>0</td>
</tr>
<tr>
<td>Patient Pain (0-10 cm)</td>
<td>0</td>
</tr>
<tr>
<td>Mean HAQ (0-3)</td>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Tool</th>
<th>Result</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAS</td>
<td>0.00</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Clinical Variable</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient Global Activity (0-10.0 cm)</td>
<td>0</td>
</tr>
<tr>
<td>Patient Pain (0-10 cm)</td>
<td>0</td>
</tr>
<tr>
<td>Mean HAQ II (0-3)</td>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Tool</th>
<th>Result</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAS II</td>
<td>0.00</td>
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</tr>
</tbody>
</table>

### Disease Activity

<table>
<thead>
<tr>
<th>Range</th>
<th>Remission</th>
<th>Low</th>
<th>Moderate</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.00 - 0.25</td>
<td>0.26 - 3.70</td>
<td>3.71 - 7.99</td>
<td>8.00 - 10.00</td>
<td></td>
</tr>
</tbody>
</table>
Use of ESR and CRP as measures of RA disease activity

- Single biomarkers, such as CRP and ESR, are incomplete measures of RA disease activity.

- CRP and ESR levels were low in the majority of 9,135 patients with active RA (CDAI >2.8) studied from the CORRONA registry.

- CDAI = clinical disease activity index;
- CORRONA = Consortium of Rheumatology Researchers of North America
Guide to the Vectra DA Test Report

**VCKTRA DA SCORE**

Vectra DA measures the concentrations of 12 serum proteins. An algorithm is applied to these concentrations to calculate a quantitative Vectra DA disease activity score ranging from 1 to 100.

**CLINICAL THRESHOLDS**


<table>
<thead>
<tr>
<th>Disease Activity Level</th>
<th>Vectra DA</th>
<th>DAS28CRP</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>≥44</td>
<td>≥4.1</td>
</tr>
<tr>
<td>Moderate</td>
<td>≥29 and ≤44</td>
<td>≥2.7 and ≤4.1</td>
</tr>
<tr>
<td>Low</td>
<td>≤29</td>
<td>≤2.7</td>
</tr>
<tr>
<td>Remission</td>
<td>≤25</td>
<td>≤2.3</td>
</tr>
</tbody>
</table>

**TEST RESULTS**

**Vectra DA Score = 19** (95% Range*: 16.5 – 21.5)

**SPECFIC COLLECTION DATE**

<table>
<thead>
<tr>
<th>Vectra DA Score</th>
<th>SPECIFIC COLLECTION DATE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>20-29</td>
</tr>
<tr>
<td>Moderate</td>
<td>30-44</td>
</tr>
<tr>
<td>High</td>
<td>45-100</td>
</tr>
</tbody>
</table>

**Clinical Validation:** Vectra DA was validated in adults with rheumatoid arthritis (RA), 230 who previously tested positive for rheumatoid factor (RF) and/or antibodies to cyclic citrullinated peptide (anti-CCP) and 141 who tested negative for both RF and anti-CCP. The performance of the test may differ between these two populations. Curtis et al. Arthritis Care Res. 2012; 64 Suppl 1: 1010-1095. [Epub ahead of print]. The Vectra DA disease activity thresholds shown in the graph reflect the Vectra DA score equivalents to DAS28CRP cutoffs of 2.67 (low to moderate) and 3.09 (moderate to high), respectively (House et al. Ann Rheum Dis. 2007;66: 407-409), and were calculated by converting the DAS28 scale (0-9.4) to the Vectra DA scale (1 to 100).

**Vectra DA Disease Activity Levels:** Low: 1 to 29 Moderate: 30 to 44 High: 45 to 100

**Test Description:** Vectra DA measures the concentrations of 12 serum proteins. An algorithm is applied to these concentrations to calculate a quantitative disease activity score ranging from 1 to 100. Test results are intended to aid in the assessment of disease activity in RA patients when used in conjunction with standard clinical assessment. This test is not intended or validated to diagnose RA.


**LONGITUDINAL RESULTS**

Lines shown between reported Vectra DA scores are for illustrative purposes only and do not represent actual test scores.

**INTENDED USE**

Vectra DA is intended to be used in conjunction with standard clinical practice for the assessment of disease activity in RA patients. It is not intended or validated to diagnose RA.

**VALIDATION POPULATION**

Vectra DA is validated for use in adults diagnosed with rheumatoid arthritis (RA).

95% RANGE

The 95% range is a measure of the analytical precision of the Vectra DA score, established by running specimens through the test process multiple times.
### PATIENT AND SPECIMEN INFORMATION

<table>
<thead>
<tr>
<th>Patient Name:</th>
<th>Patient Patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient ID:</td>
<td>PT000702</td>
</tr>
<tr>
<td>Sex:</td>
<td>Female</td>
</tr>
<tr>
<td>DOB:</td>
<td>Jul-07-1992</td>
</tr>
<tr>
<td>TRF ID:</td>
<td>TR11050161CI</td>
</tr>
<tr>
<td>Collection Date:</td>
<td>Sep-05-2012</td>
</tr>
<tr>
<td>Receipt Date:</td>
<td>Sep-05-2012</td>
</tr>
</tbody>
</table>

### PHYSICIAN AND REPORT INFORMATION

<table>
<thead>
<tr>
<th>Ordering MD:</th>
<th>Doctor in Doctor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinic:</td>
<td>ABC Clinic</td>
</tr>
<tr>
<td>Phone:</td>
<td>656-555-5555</td>
</tr>
<tr>
<td>Fax:</td>
<td>877-743-8840</td>
</tr>
<tr>
<td>Report Date:</td>
<td>Sep-09-2012</td>
</tr>
</tbody>
</table>

### INDIVIDUAL BIOMARKER RESULTS

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Result</th>
<th>Units</th>
<th>RA Range</th>
<th>RA Percentile</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adhesion Molecules</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VCAM-1</td>
<td>0.54</td>
<td>μg/mL</td>
<td>0.35-1.1</td>
<td>40%</td>
</tr>
<tr>
<td>Growth Factors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EGF1</td>
<td>260</td>
<td>pg/mL</td>
<td>21-380</td>
<td>81%</td>
</tr>
<tr>
<td>VEGF-A</td>
<td>460</td>
<td>pg/mL</td>
<td>83-700</td>
<td>84%</td>
</tr>
<tr>
<td>Cytokine-related Proteins</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IL-6</td>
<td>5.1</td>
<td>pg/mL</td>
<td>2.2-100</td>
<td>20%</td>
</tr>
<tr>
<td>TNF-RI</td>
<td>1.3</td>
<td>ng/mL</td>
<td>1.1-4.5</td>
<td>6%</td>
</tr>
<tr>
<td>Matrix Metalloproteinases</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MMP-1</td>
<td>5.7</td>
<td>ng/mL</td>
<td>3.1-39</td>
<td>18%</td>
</tr>
<tr>
<td>MMP-3</td>
<td>51</td>
<td>ng/mL</td>
<td>9.2-130</td>
<td>79%</td>
</tr>
<tr>
<td>Skeletal-related Proteins</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>YKL-40</td>
<td>28</td>
<td>ng/mL</td>
<td>26-440</td>
<td>4%</td>
</tr>
<tr>
<td>Hormones</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leptin</td>
<td>14</td>
<td>ng/mL</td>
<td>1.0-45</td>
<td>63%</td>
</tr>
<tr>
<td>Resistin</td>
<td>4.1</td>
<td>ng/mL</td>
<td>3.6-19</td>
<td>5%</td>
</tr>
<tr>
<td>Acute Phase Proteins</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SAA</td>
<td>1.6</td>
<td>μg/mL</td>
<td>0.64-100</td>
<td>10%</td>
</tr>
<tr>
<td>CRP</td>
<td>2.3</td>
<td>mg/L</td>
<td>0.24-77</td>
<td>29%</td>
</tr>
</tbody>
</table>

* Those ranges were established using 512 RA patient samples from the InforM study (Ann Rheum Dia 2016; 69, Suppl 3; 657), except for leptin for which 112 non-disease RA patient samples were used.

† Subject's biomarker level relative to levels in RA patient specimens from which the RA range was determined.

§ Inversely correlated with disease activity.

Please note: These are signs of significant figures, which are required inputs into the algorithm used to calculate the Vectra DA Score. Clinical interpretation of individual biomarker levels, which have different weights in the Vectra DA algorithm, has not been established.

The Vectra DA test is intended for clinical use. It was developed and its performance characteristics determined by Crescendo Bioscience, Inc. The Crescendo Bioscience Clinical Laboratory is certified under the Clinical Laboratory Improvement Act of 1988 (CLIA) as qualified to perform high complexity clinical testing.

Crescendo Bioscience Clinical Laboratory • 341 Cyster Point Boulevard • South San Francisco, CA 94080 • www.crescendo.com

ML-TR-06 5/13
Laboratory Director: Russell Karczewski, MD. GAD Pathologist, MD. PhD. (NY). Laboratory ID. No. CLF039205 CLIA No. 50H0654

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ML_VTRG-08 05/13
RA: Goals of Treatment

- Reduce pain, stiffness and fatigue
- Improve quality of life
- Prevent joint destruction
- Maintain full function
- Reduce CV events
- Prolong lifespan
RA: Strategy for Treatment

1 - Treat early
– To prevent damage and disability
– Start DMARD within six weeks of diagnosis or symptoms

2 - Treat hard
– Maximal efficacious dose that is tolerated by the patient
– Rapid escalation of DMARD (e.g., MTX to 20 mg/wk by wk 8)
RA: Strategy for Treatment

3 - Treat with combination of DMARDs (where appropriate)
- Combination therapy is consistently more effective than monotherapy
- Does it matter if combination is started immediately or achieved by step-up therapy?
- Is one combination better than another?
- Should all patients be treated with combination tx?

- Presence of bad prognostic indices can guide decision:
  ↑↑ swollen joints, ↑↑ ESR/CRP, ↑↑ RF/CCP, erosions at baseline
RA: Strategy for Treatment

4 - Treat with a targeted goal

– Aim for remission of disease activity
– Or, at least, low disease activity
What is Remission?

• ACR/EULAR recommended definition, (Felson et al, Arthritis & Rheumatism 2011)

  – Scores must all be < 1:
    Tender joint count
    Swollen joint count
    CRP (mg/dL)
    Patient global assessment

  – Or SDAI < 3.3
# Current Treatments for RA

<table>
<thead>
<tr>
<th>Conventional synthetic (cs) DMARDs</th>
<th>Biologic (b) DMARDs</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Methotrexate</td>
<td>- Cytokine inhibitors</td>
</tr>
<tr>
<td>- Sulfasalazine</td>
<td>- Anti-TNF</td>
</tr>
<tr>
<td>- Hydroxychloroquine</td>
<td>- Anti-IL-6R</td>
</tr>
<tr>
<td>- Leflunomide</td>
<td>- (Anti-IL-1)</td>
</tr>
</tbody>
</table>

**Targeted synthetic (ts) DMARDs**

- JAK kinase inhibitors

**Biologic (b) DMARDs**

- Cytokine inhibitors
  - Anti-TNF
  - Anti-IL-6R
  - (Anti-IL-1)

- Cellular depletion/inhibitors
  - B cell depleting
  - T cell costimulatory inhibitor
RA Treatment Algorithm

• Initially, MTX monotherapy unless contraindication
• If inadequate response, second DMARD added
• If residual disease activity is:
  – mild, add non-biologic
  – moderate, add non-biologic or biologic
  – severe, add targeted therapy (non-biologic or biologic)

• ‘Make the punishment fit the crime’
Biologic DMARDs: Cytokine Inhibitors

• Anti-TNF
  – Etanercept, infliximab, adalimumab, certolizumab, golimumab plus Biosimilars
  – All antibodies except etanercept (soluble TNF receptor)
  – Effective as monotherapy or with MTX and other csDMARDs
  – Efficacy: similar despite mechanism (Ab vs receptor)
  – Safety: more infectious risk with high dose infliximab
  – Immunogenicity: highest with infliximab → use w/MTX

• Do not combine two biologic DMARDs
Biologic DMARDs: Cytokine Inhibitors

Anti-IL-6 Agents: Tocilizumab, Sarilumab

– Effective as monotherapy
– Effective in MTX inadequate responders
– Effective in TNF inadequate responders
– Safety: elevates lipids, GI perforations
Biologic DMARDs: Cell Based Inhibitors

• B cell depleting agent: Rituximab
  – Immunogenicity: high, use with MTX (+steroids)
  – Efficacy: better in combo w/ MTX than monotherapy
  – Safety: rare risk of Progressive Multifocal Leukoencephalopathy (PML); ?hypogamma?
Biologic DMARDs: Cell Based Inhibitors

• T cell co-stimulatory inhibitor: Abatacept
  – Efficacy: monotherapy or in combination with csDMARDs
  – Safety: TB risk appears to be lower than w/TNF inhibitors
  – Available IV and SC
Targeted synthetic (ts) DMARDs: JAK Inhibitors

- **Tofacitinib**: inhibits Janus kinase 1/3 > 2
- **Baricitinib**: inhibits JAK-1, JAK-2 > JAK-3 and Tyk-2
- Oral; Quick onset of action
- Effective as monotherapy or in combination with other non-biologic DMARDs
- Potential side effects: anemia (JAK-2), lipid elevations, neutropenia, LFT elevations
JAK Inhibitors: Toxicities

• Effects on hematopoietic cell lineages
  – Decrease in PMNs related to reduction in inflammation?
  – Anemia, decrease in NK cells related to JAK-2 inhibition
  – Response to immunizations adequate (influenza, pneumococcal)
  – Herpes zoster

• Elevation of lipids

• Thrombotic events (DVTs)
JAK Inhibitors: Second Generation

• Goal: target JAK-1 with more specificity.
  – Filgotinib
  – Upadacitinib

• But arguably less specific at higher doses.
Biosimilars (Bridges SL et al, A&R 2018)

• Legitimate copy of a biopharmaceutical (the ‘reference product’ or the ‘bio-originator’) that has undergone
  – Rigorous comparison to bio-originator
  – Head to head clinical trial with bio-originator
  – Approval by a regulatory agency (FDA)

• Small chemical drugs can be exactly copied; biosimilars cannot

• Biosimilars produced by recombinant DNA technology
  – Must be identical in primary structure
  – Must be highly similar in secondary, tertiary and quaternary structure to their reference products
FDA Approved Biosimilars for Rheumatic Diseases

<table>
<thead>
<tr>
<th>Biosimilar</th>
<th>Reference Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adalimumab-atto (Amjevita)</td>
<td>Adalimumab (Humira)</td>
</tr>
<tr>
<td>Adalimumab-adbm (Cyltezo)</td>
<td>Adalimumab (Humira)</td>
</tr>
<tr>
<td>Adalimumab-adaz (Hyrimoz)</td>
<td>Adalimumab (Humira)</td>
</tr>
<tr>
<td>Etanercept-szzs (Erelzi)</td>
<td>Etanercept (Enbrel)</td>
</tr>
<tr>
<td>Infliximab-abda (Renflexis)</td>
<td>Infliximab (Remicade)</td>
</tr>
<tr>
<td>Infliximab-dyyb (Inflectra)</td>
<td>Infliximab (Remicade)</td>
</tr>
<tr>
<td>Infliximab-qbtx (Ixifi)</td>
<td>Infliximab (Remicade)</td>
</tr>
</tbody>
</table>
Biosimilars: Questions

• How much cheaper compared to the bio-originators?
  – Savings may be offset by manufacturer discounts of bio-originators
  – If lower cost drugs allow more patients to be treated, overall expenditures on biologics may then rise.

• Will they become first line biologic therapies? Possibly, for patients naïve to the bio-originator in question
Biosimilars: Questions

• For patients on bio-originators with stable disease activity, will payors or pharmacy benefit managers (PBMs) force switching to cheaper biosimilars?

  – NOR-SWITCH (Jorgensen KK, Lancet 2017) study showed no greater toxicity or loss of efficacy when switched from infliximab to CT-P13

  – FDA requires studies with multiple switches within individuals to justify ‘interchangeability’

  – Laws regarding ‘interchangeability’ in the US will be determined by state-by-state legislation
<table>
<thead>
<tr>
<th>DMR/DCS</th>
<th>CONTINUE these medications through</th>
<th>Dosing Interval</th>
<th>Continuation/Withdrawal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methotrexate</td>
<td>Weekly</td>
<td>Continue</td>
<td></td>
</tr>
<tr>
<td>Sulfasalazine</td>
<td>Once or twice daily</td>
<td>Continue</td>
<td></td>
</tr>
<tr>
<td>Hydroxychloroquine</td>
<td>Once or twice daily</td>
<td>Continue</td>
<td></td>
</tr>
<tr>
<td>Leflunomide (Lemtra)</td>
<td>Daily</td>
<td>Continue</td>
<td></td>
</tr>
<tr>
<td>Doxycycline</td>
<td>Daily</td>
<td>Continue</td>
<td></td>
</tr>
</tbody>
</table>

**BIOLOGIC AGENTS:** STOP these medications prior to surgery and schedule surgery at the end of the dosing cycle. RESUME medications at minimum 14 days after surgery in the absence of wound healing problems, surgical site infection, or systemic infection.

<table>
<thead>
<tr>
<th>DMR/DCS</th>
<th>Dosing Interval</th>
<th>Schedule Surgery (relative to last biologic agent dose administered) during</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adalimumab (Humira)</td>
<td>Weekly or every 2 weeks</td>
<td>Week 2 or 3</td>
</tr>
<tr>
<td>Etanercept (Enbrel)</td>
<td>Weekly or twice weekly</td>
<td>Week 2</td>
</tr>
<tr>
<td>Golimumab (Simponi)</td>
<td>Every 4 weeks (Q4) or every 8 weeks (Q8)</td>
<td>Week 8</td>
</tr>
<tr>
<td>Infliximab (Remicsda)</td>
<td>Every 4, 6, or 8 weeks</td>
<td>Week 5, 7, or 9</td>
</tr>
<tr>
<td>Alefacept (Actimmune)</td>
<td>Monthly (QM) or weekly (QW)</td>
<td>Week 5</td>
</tr>
<tr>
<td>Certolizumab (Cimzia)</td>
<td>Every 2 or 4 weeks</td>
<td>Week 4 or 8</td>
</tr>
<tr>
<td>Rituximab (Rituxan)</td>
<td>2 doses 1 week apart every 4-8 months</td>
<td>Month 7</td>
</tr>
<tr>
<td>Trastuzumab (Herceptin)</td>
<td>Every 3 weeks (Q3) or every 4 weeks (Q4)</td>
<td>Week 3 or 5</td>
</tr>
<tr>
<td>Anakinra (Kineret)</td>
<td>Daily</td>
<td>Day 2</td>
</tr>
<tr>
<td>Seucicliumab (Stelara)</td>
<td>Every 4 weeks</td>
<td>Week 5</td>
</tr>
<tr>
<td>Ustekinumab (Stelara)</td>
<td>Every 12 weeks</td>
<td>Week 13</td>
</tr>
<tr>
<td>Belimumab (Belvyra)</td>
<td>Every 4 weeks</td>
<td>Week 5</td>
</tr>
<tr>
<td>Tocilizumab (Actemra): STOP this medication 7 days prior to surgery.</td>
<td>Daily or twice daily</td>
<td>7 days after last dose</td>
</tr>
</tbody>
</table>

**SEVERE SLE-SPECIFIC MEDICATIONS:** CONTINUE these medications in the perioperative period.

<table>
<thead>
<tr>
<th>DMR/DCS</th>
<th>Dosing Interval</th>
<th>Continuation/Withdrawal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mycophenolate mofetil</td>
<td>Twice daily</td>
<td>Continue</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>Daily or twice daily</td>
<td>Continue</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>Twice daily</td>
<td>Continue</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>Twice daily (IV and PO)</td>
<td>Continue</td>
</tr>
</tbody>
</table>

**NOT SEVERE SLE; DISCONTINUE these medications 1 week prior to surgery:**

<table>
<thead>
<tr>
<th>DMR/DCS</th>
<th>Dosing Interval</th>
<th>Continuation/Withdrawal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mycophenolate mofetil</td>
<td>Twice daily</td>
<td>Withdraw</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>Daily or twice daily</td>
<td>Withdraw</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>Twice daily</td>
<td>Withdraw</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>Twice daily (IV and PO)</td>
<td>Withdraw</td>
</tr>
<tr>
<td>DMARDs</td>
<td>Dosing Interval</td>
<td>Continue/Withhold</td>
</tr>
<tr>
<td>------------------</td>
<td>-------------------------</td>
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</tr>
<tr>
<td>Hydroxychloroquin</td>
<td>Once or twice daily</td>
<td>Continue</td>
</tr>
<tr>
<td>Leflunomide</td>
<td>Daily</td>
<td>Continue</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>Daily</td>
<td>Continue</td>
</tr>
</tbody>
</table>
BIOLOGICS

- **STOP** these medication prior to surgery at the end of dosing cycle and schedule surgery at the end of dosing cycle.

- **RESUME** medications at minimum 14 days after surgery in the absence of wound healing problems. Surgical site infections or systemic infections.
<table>
<thead>
<tr>
<th>BIOLOGICS</th>
<th>Dosing Interval</th>
<th>Schedule Surgery during (Relative to last biologic agent dose administered)</th>
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<tr>
<td>Etanercept (Enbrel)</td>
<td>Weekly or every 2 weeks</td>
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<td>Weekly or twice weekly</td>
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</tr>
<tr>
<td>Golimumab (Simponi)</td>
<td>Every 4 weeks SQ</td>
<td>Week 5</td>
</tr>
<tr>
<td></td>
<td>Every 8 weeks IV</td>
<td>Week 9</td>
</tr>
<tr>
<td>Infliximab (Remicade)</td>
<td>Every 4, 6 or 8 weeks</td>
<td>Week 5, 7 or 9</td>
</tr>
<tr>
<td>Abatacept (Orencia)</td>
<td>Monthly IV or Weekly SQ</td>
<td>Week 5</td>
</tr>
<tr>
<td></td>
<td>Weekly SQ</td>
<td>Week 2</td>
</tr>
<tr>
<td>Certolizumab (Cimzia)</td>
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<td>Week 3 or 5</td>
</tr>
<tr>
<td>Tocilizumab (Actemra)</td>
<td>Every week SQ</td>
<td>Week 2</td>
</tr>
<tr>
<td></td>
<td>Every 4 weeks IV</td>
<td>Week 5</td>
</tr>
<tr>
<td>Anakinra (Kinert)</td>
<td>Daily</td>
<td>Day 2</td>
</tr>
<tr>
<td>Secukinumab (Cosentyx)</td>
<td>Every 4 weeks</td>
<td>Week 5</td>
</tr>
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<td>Ustekinumab (Stelara)</td>
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<tr>
<td>Tofacintinib (Xeljanz)</td>
<td>Daily or twice daily</td>
<td>7 days</td>
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<tr>
<td>Rituximab (Rituxan)</td>
<td>2 doses 2 week apart every 4-6 months</td>
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</tr>
</tbody>
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SLE-specific medications

<table>
<thead>
<tr>
<th>DMARDs</th>
<th>Dosing Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mycophenolate Mofetil</td>
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<tr>
<td>Azathioprine</td>
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</tr>
<tr>
<td>Cyclosporine</td>
<td>Twice daily</td>
</tr>
<tr>
<td>Tacrolimus (IV or PO)</td>
<td>Twice daily</td>
</tr>
</tbody>
</table>

Severe SLE – CONTINUE these medications in the perioperative period

Non severe SLE – DISCONTINUE these medications 1 week prior to surgery
Myopathy - Diagnostic Testing

- Acute phase reactants unreliable
- Muscle Enzymes
  - CPK: elevated >65%; >10% MB fraction is possible
  - Muscle specific- Aldolase, Troponin
  - AST > LDH > ALT
    - watch out for rising creatinine (ATN) and myoglobinuria
- Serologic Tests
  - ANA (+) 60%, nonspecific
  - Myositis specific antibodies
Myopathy - Diagnostic Testing

- Electromyogram (EMG)
  - increased insertional activity
  - low amplitude, polyphasic potentials
  - positive sharp waves
  - (beware of neuropathic changes)

- Magnetic Resonance Imaging detects increased water signal, fibrous tissue, infiltration, calcification

- Muscle Biopsy
  - Send to the neuropathologist - 85% Sensitive.
  - Biopsy the involved muscle (MRI guided)
  - Avoid EMG/injection sites or sites of trauma
**Myositis-specific autoantibodies**

<table>
<thead>
<tr>
<th>Autoantibodies</th>
<th>Clinical features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-ARS (antisynthetase)</td>
<td>AS syndrome with moderate-to-serve muscle weakness with high muscle enzyme levels, RP, mechanic’s hands, fever, arthritis, and ILD</td>
</tr>
<tr>
<td>Anti-Jo-1 (20-30%)</td>
<td>Chronic continuous disease course, with clinical symptoms for &gt;two years after diagnosis; mean five-year survival rate = 65%, usually due to ILD; AS syndrome features</td>
</tr>
<tr>
<td>Anti-PL-7 (&lt;5)</td>
<td>AS syndrome with higher frequency of ILD</td>
</tr>
<tr>
<td>Anti-PL-12 (&lt;5)</td>
<td>AS syndrome with higher frequency of ILD</td>
</tr>
<tr>
<td>Anti-EJ (&lt;5)</td>
<td>Dermatomyositis and ILD</td>
</tr>
<tr>
<td>Anti-OJ (&lt;5)</td>
<td>Myositis and ILD</td>
</tr>
<tr>
<td>Anti-KS (&lt;1)</td>
<td>ILD with less myositis</td>
</tr>
<tr>
<td>Anti-Ha (&lt;1)</td>
<td>NA</td>
</tr>
<tr>
<td>Anti-Zo (&lt;1)</td>
<td>Myositis and ILD</td>
</tr>
<tr>
<td>Anti-SRP</td>
<td>Acute onset NM with severe weakness, high CK, cardiac involvement; refractory to treatment</td>
</tr>
<tr>
<td>Anti-Mi-2</td>
<td>Adult DM and JDM with hallmark cutaneous disease, milder myositis with good response to treatment</td>
</tr>
</tbody>
</table>
# Myositis-specific autoantibodies

<table>
<thead>
<tr>
<th>Autoantibodies</th>
<th>Clinical features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-TIF1-y (anti-p155/140)</td>
<td>CAM in adult DM; severe cutaneous disease in adult DM and JDM</td>
</tr>
<tr>
<td>Anti-SAE</td>
<td>Adult DM; may present with CADM first</td>
</tr>
<tr>
<td>Anti-MDA5 (anti-CADM140)</td>
<td>CADM; rapidly progressive ILD</td>
</tr>
<tr>
<td>Anti-NXP-2</td>
<td>Predominantly JDM with subcutaneous edema, calcinosis, and severe muscle disease with contractures; increased risk of cancer in some adult DM studies</td>
</tr>
<tr>
<td>Anti-HMGCR</td>
<td>NM; associated with statin use in adults; severe proximal muscle weakness; partially responsive to immunosuppressive medications; better response to IVIg</td>
</tr>
<tr>
<td>Anti-cN-1A (Mup44, NT5c1A)</td>
<td>IBM; higher mortality risk</td>
</tr>
</tbody>
</table>

ARS=aminoacyl-tRNA synthetase; AS syndrome=antisynthetase syndrome; RP=Raynaud’s phenomenon; ILD=interstitial lung disease; SRP=signal recognition particle; T1F1-y=transcriptional intermediary factory 1-gamma; NXP-2=nuclear matrix protein-2; SAE=small-ubiquitin-like modifier activating enzyme; MDA5=melanoma-differentiation associated gene 5; CAM=cancer-associated myositis; CADM-clinically amyopathic DM; NA-not applicable/no data.
Statin Induced Myopathy/Myositis

- More common in elderly, (those on myopathic meds)
  - Cyclosporine A, gemfibrozil, itraconazole, erthromycin, clarithromycin, protease inhibitor
- Onset – 1st 6 mos; Sxs last 1-6 mos on discontinuation
- LFT elevations < 3 fold – up to 50%
- Risk of rhabdomyolysis 5-18% – Incidence: 3.5 cases /100,000 patient years with standard doses
- Renal dysfunction 4%
- Rx: D/c, Lowest dose, d/c concomitant meds, lifestyle change
- 14 reports of Statin related IIM: 10 PM, 14 DM, and 63 cases with necrotizing myopathies (Anti-HMGCR ab)

Statin Induced Immune Myopathy

- Background: Statin use can result in a self limited myopathy. In some patients statin exposure may trigger a chronic immune mediated necrotizing myopathy.

- 6% of the 750 patients in the Johns Hopkins Myositis Center cohort with IMNM shown to have 100kD autoantibody against 3 hydroxy 3 methylglutaryl coenzyme reductase (HMGCR)
  - Proximal weakness, mean CK 9718, EMG myopathy, necrotizing myositis on biopsy, 92% statin exposure (age >50)

- In vitro, statins increase HMGCR expression in muscle cells

- Statins upregulate HMGCR expression; autoantigen in IMNM

- Regenerating muscle cells express high levels of HMGCR, which may sustain the immune response even after statins are discontinued.

Inclusion Body Myositis (IBM)

- Bimodal age distribution, may be hereditary
- Slow onset, progressive (asymmetric) weakness
- Painless, distal and proximal (asymmetric) weakness, dysphagia
- Normal or mildly elevated CPK (usually below 2,000 IU/ml)
- Poor response to corticosteroids
- Dx: light microscopy normal or show CD8+ lymphocytes. Tubulofilamentous inclusion bodies on EM
- Anti-cN-1A (Mup44, NT5c1A)
- New Rx: Alemtuzumab (Campath) in inclusion body myositis

Necrotizing Myopathy

• Necrotizing myopathy is rare (but increasing) entity & may be associated with myositis specific Abs:
  – anti-HMGCR Abs from Statins
  – Anti- PL-12 Abs
  – Anti- PL-17 Abs
  – Signal Recognition Particle Ab

• Auto Antibody markers have *clinical and prognostic* importance

• How do you order them?

  – RDL laboratories
  – OMRF (Oklahoma Medical Research Foundation)
  – Quest Diagnostics
  – Mayo Medical Laboratories
  – ARUP Laboratories
Inflammatory Myositis - Treatment

- Corticosteroids: 60-80 mg/day (80% respond within 12 weeks)
- Steroid resistant:
  - Methotrexate
  - Azathioprine
  - Leflunomide, Mycophenolate, Tacrolimus
- IVIG, Cyclosporine, Chlorambucil, Sirolimus
- No response to apheresis, TNF inhibitors

Neth J Med 2011;69:410-21
## SLE: CLASSIFICATION CRITERIA
1997 update of 1982 ACR criteria

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malar rash</td>
<td>Fixed erythema, flat or raised, over the malar eminences, tending to spare the nasolabial folds</td>
</tr>
<tr>
<td>Photosensitivity</td>
<td>Skin rash as a result of unusual reaction to sunlight, by patient history or physician observation</td>
</tr>
<tr>
<td>Discoid rash</td>
<td>Erythematous raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring may occur in older lesions</td>
</tr>
<tr>
<td>Oral ulcers</td>
<td>Oral or nasopharyngeal ulceration, usually painless, observed by a physician</td>
</tr>
<tr>
<td>Arthritis</td>
<td>Nonerosive arthritis involving 2 or more peripheral joints, characterized by tenderness, swelling, or effusion</td>
</tr>
<tr>
<td>Serositis</td>
<td>Pleuritis - convincing history of pleuritic pain or rubbing heard by a physician or evidence of pleural effusion OR Pericarditis - documented by EKG, rub, or evidence of pericardial effusion</td>
</tr>
<tr>
<td>Renal disorder</td>
<td>Persistent proteinuria greater than 500 mg/24 hours or greater than 3+ if quantitation not performed OR Cellular casts - may be red cell, hemoglobin, granular, tubular, or mixed</td>
</tr>
<tr>
<td>Neurologic disorder</td>
<td>Seizures OR psychosis - in the absence of offending drugs or known metabolic derangements (uremia, ketoacidosis, or electrolyte imbalance)</td>
</tr>
<tr>
<td>Hematologic disorder</td>
<td>Hemolytic anemia - with reticulocytosis OR Lymphopenia - less than 1500/mm³ on two or more occasions OR Thrombocytopenia - less than 100,000/mm³ (in the absence of offending drugs)</td>
</tr>
<tr>
<td>ANA</td>
<td>An abnormal titer of antinuclear antibody by immunofluorescence or an equivalent assay at any point in time and in the absence of drugs known to be associated with &quot;drug-induced lupus&quot; syndrome</td>
</tr>
<tr>
<td>Immunologic disorders</td>
<td>Anti-DNA - antibody to native DNA in abnormal titer OR Anti-Sm - presence of antibody to Sm nuclear antigen OR Positive finding of antiphospholipid antibody based on an abnormal serum level of IgG or IgM antiphospholipid antibodies, on a positive test result for lupus anticoagulant using a standard method, or on a false positive serologic test for syphilis known to be positive for at least six months and confirmed by Treponema pallidum immobilization or fluorescent treponemal antibody absorption test</td>
</tr>
</tbody>
</table>
## SLICC criteria for the classification of SLE

<table>
<thead>
<tr>
<th>Clinical criteria</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute cutaneous lupus</td>
<td>Lupus malar rash (do not count if malar discoid); bullous lupus; toxic epidermal necrolysis variant of SLE; maculopapular lupus rash; photosensitive lupus rash (in the absence of dermatomyositis); OR subacute cutaneous lupus (nonindurated psoriaform and/or annular polycyclic lesions that resolve without scarring, although occasionally with postinflammatory dyspigmentation or telangiectasias)</td>
</tr>
<tr>
<td>Chronic cutaneous lupus</td>
<td>Classic discoid rash; localized (above the neck); generalized (above and below the neck); hypertrophic (verrucous) lupus; lupus panniculitis (profundus); mucosal lupus; lupus erythematous tibial; chilblains lupus; OR discoid lupus/lichen planus overlap</td>
</tr>
<tr>
<td>Nonscarring alopecia</td>
<td>Diffuse thinning or hair fragility with visible broken hairs (in the absence of other causes such as alopecia areata, drugs, iron deficiency, and androgenic alopecia)</td>
</tr>
<tr>
<td>Oral or nasal ulcers</td>
<td>Palate, buccal, tongue, OR nasal ulcers (in the absence of other causes, such as vasculitis, Behçet's disease, infection (herpesvirus), inflammatory bowel disease, reactive arthritis, and acidic foods)</td>
</tr>
<tr>
<td>Joint disease</td>
<td>Synovitis involving 2 or more joints, characterized by swelling or effusion OR Tenderness in 2 or more joints and at least 30 minutes of morning stiffness</td>
</tr>
<tr>
<td>Serositis</td>
<td>Typical pleurisy for more than 1 day, pleural effusions, or pleural rub, OR Typical pericardial pain (pain with recumbency improved by sitting forward) for more than 1 day, pericardial effusion, pericardial rub, or pericarditis by electrocardiography in the absence of other causes, such as infection, uremia, and Dressler's syndrome</td>
</tr>
<tr>
<td>Renal</td>
<td>Urine protein-to-creatinine ratio (or 24-hour urine protein) representing 500 mg protein/24 hours, OR Red blood cell casts</td>
</tr>
<tr>
<td>Neurologic</td>
<td>Seizures; psychosis; mononeuropathy multiplex (in the absence of other known causes such as primary vasculitis); myelitis; peripheral or cranial neuropathy (in the absence of other known causes such as primary vasculitis, infection, and diabetes mellitus); OR acute confusional state (in the absence of other causes, including toxic/metabolic, uremia, drugs)</td>
</tr>
<tr>
<td>Hemolytic anemia</td>
<td>Hemolytic anemia</td>
</tr>
<tr>
<td>Leukopenia or lymphopenia</td>
<td>Leukopenia (&lt;4000/mm³ at least once) (in the absence of other known causes such as Felty's syndrome, drugs, and portal hypertension), OR</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>Thrombocytopenia (&lt;100,000/mm³) at least once in the absence of other known causes such as drugs, portal hypertension, and thrombotic thrombocytopenic purpura</td>
</tr>
</tbody>
</table>
## SLICC criteria for the classification of SLE

<table>
<thead>
<tr>
<th>Immunologic criteria</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANA</td>
<td>ANA level above laboratory reference range</td>
</tr>
<tr>
<td>Anti-dsDNA</td>
<td>Anti-dsDNA antibody level above laboratory reference range (or &gt;twofold the reference range if tested by ELISA)</td>
</tr>
<tr>
<td>Anti-Sm</td>
<td>Presence of antibody to Sm nuclear antigen</td>
</tr>
<tr>
<td>Antiphospholipid</td>
<td>Antiphospholipid antibody positivity as determined by any of the following: positive test result for lupus anticoagulant; false-positive test result for rapid plasma reagin; medium- or high-titer anticardiolipin antibody level (IgA, IgG, or IgM); or positive test result for anti-β2-glycoprotein I (IgA, IgG, or IgM)</td>
</tr>
<tr>
<td>Low complement</td>
<td>Low C3; low C4; <strong>OR</strong> low CH50</td>
</tr>
<tr>
<td>Direct Coombs' test</td>
<td>Direct Coombs' test in the absence of hemolytic anemia</td>
</tr>
</tbody>
</table>
SLE
ASSESSMENT OF DISEASE ACTIVITY AND SEVERITY

• **Disease activity**: manifestations of the underlying inflammatory process at a point in time in terms of magnitude and intensity.

• **Disease severity**: type and level of organ dysfunction and its consequences, (mild, moderate, severe).

• **Damage**: degree of irreversible organ dysfunction
SLE
ASSESSMENT OF DISEASE ACTIVITY AND SEVERITY

• In clinical practice, disease activity and severity are assessed using a combination of:
  • clinical history,
  • physical examination,
  • laboratory and serologic studies
  • organ-specific tests
SLE
ASSESSMENT OF DISEASE ACTIVITY AND SEVERITY

• During clinical history and physical examination, distinguish between:

  • active features of SLE
  • chronic damage
  • drug toxicities
  • comorbidities such as infections, metabolic, neurologic, cardiovascular or other conditions.
ASSESSMENT OF DISEASE ACTIVITY AND SEVERITY
Laboratory evaluation and Serologic studies

• CBC: To look for cytopenias that could be manifestation of disease or drug toxicity.
• ESR: Generally high in SLE. Could correlate with disease activity.
• CRP: is not as high as ESR. Very high CRP in SLE patients generally suggests infection.
• Urinalysis: look for hematuria, proteinuria, cellular casts.
• Protein to creatinine ratio on spot urine: To quantify proteinuria. Easy to perform compared to 24 hr urinary collection that is subject to add errors of collection.
• Serum creatinine and calculated eGFR: to assess the renal function.
• Complement level C3 and C4: Low levels suggest lupus disease activity. Especially lupus nephritis due to consumption. High complement levels can also be seen with active lupus as part of acute phase reactants.
• dsDNA Antibodies: Fluctuate with disease activity especially glomerulonephritis.
• Titers of other antibodies do not correlate with disease activity.
Scoring systems for global disease activity of SLE

- Systemic Lupus Erythematosus Disease Activity Index-2K (SLEDAI-2K)
- Revised Systemic Lupus Activity Measure (SLAM-R)
- European Consensus Lupus Activity Measurement (ECLAM)
  (can assess single organ disease activity. Also provides information on multiple systems.)
- Composite assessment measures such as SRI (Systemic Lupus Erythematosus Response Index) and BICLA (BILAG-based Combined Lupus Assessment)
SLE
Damage indices

• A measure for chronic damage and has prognostic value
• Damage could be from disease activity or treatment.

• The systemic lupus international collaborating clinics American College of Rheumatology damage index (SLICC/ACR-DI) is used to measure accumulated damage that has occurred since disease onset
Pharmacologic treatment of lupus

• **Mild lupus** (skin, joint, and mucosal involvement): Hydroxychloroquine, NSAIDs, short course of low-dose prednisone ≤ 7.5 mg/day

• **Moderate lupus** (Significant but non organ threatening disease including constitutional, cutaneous, musculoskeletal, or hematologic): hydroxychloroquine, prednisone 5-15 mg /day, additional immunosuppressants such as azathioprine or methotrexate down the road as steroid sparing drugs)

• **Severe or life-threatening** (major organ involvement such as renal and CNS): Short course of IV steroids such as methylprednisolone 0.5-1 g per day for 3 days, followed by prednisone 1 mg/kg body weight. Additional immunosuppressants depending on the organ involvement include mycophenolate, cyclophosphamide, azathioprine, rituximab. Initially high-dose to achieve remission followed by lower doses for maintenance.
Hydroxychloroquine

- Recommended for all
- Improves rash and arthritis
- Increased survival: LUMINA cohort
- Reduced lipid levels (TC: -8%; LDL: -14%)
- Anti-thrombotic effects
- Reduced risk of early cumulative damage
- Flare prevention

- Pregnancy category C, no increase in congenital defects, fetal death, miscarriage or prematurity. Less maternal disease activity
  - 15 years of data
- Reduces recurrence of neonatal lupus (cardiac-NL)
- Reduces the risk of diabetes in RA
- Associated with greater reduction in HbA1c in diabetic patients with rheumatic disease

2) Cairoli E et al. Lupus 2012
3) Petri M Curr Rheumatol Rep 2011
4) Akhavan PS et al. J Rheumatol 2013
Bullseye Maculopathy

- Recommended the use of an Amsler grid
- Were prompted in part to be less restrictive than the Physicians’ Desk Reference recommendation for an eye exam every 3 months.
- Recommended a dosage of 6.5 mg/kg/day
Major Risk Factors for Toxic Retinopathy

• Daily dosage
  • HCQ >5.0 mg/kg real weight
  • CQ >2.3 mg/kg real weight
• Duration of use >5 Yrs, assuming no other risk factors
• Renal disease Subnormal glomerular filtration rate
• Concomitant drugs Tamoxifen use
• Macular disease May affect screening and susceptibility to HCQ/CQ

CQ (chloroquine); HCQ (hydroxychloroquine)

Ophthalmology, 123:1386, 2016
Clinical Examination Techniques

• Recommended Screening Tests
  Primary tests: ideally do both
  • Automated visual fields (appropriate to race)
  • SD OCT

Other objective tests (as needed or available):
  • mfERG
  • FAF

Newer tests of possible value in future
  • Microperimetry
  • Adaptive optics retinal imaging

• Not Recommended for Screening
  • Fundus examination
  • Time-domain OCT
  • Fluorescein angiography
  • Full-field ERG
  • Amsler grid
  • Color testing
  • EOG

EOG = electro-oculogram; ERG = electroretinogram; FAF = fundus autofluorescence; mfERG = multifocal electroretinogram; SD OCT = spectral-domain optical coherence tomography
Flying saucer sign

- Thinned Outer Nuclear Layer
- Loss of Photoreceptor Inner Segment / Outer Segment Junction
2016 Guidelines for Hydroxychloroquine monitoring
(Ophthalmology, 123:1386, 2016)

• Maximum dose of HCQ should be < 5.0 mg/kg actual weight
• Obtain baseline and screen annually at 5 years
• OCT and Visual fields are mainstay of screening
• Other screening options: Autofluorescence or ERG

• The goal of screening for retinopathy is not to stop valuable drugs at the first borderline abnormality, but to recognize definitive signs of toxicity at an early enough stage to prevent a loss of visual acuity
Prednisone Therapy for Lupus Nephritis
Clinical Considerations (LOE: 3C)

• When to use intravenous pulse methylprednisolone
  – Class IV or IV/V with cellular crescents and/or fibrinoid necrosis
  – Dose: 500-1000mg intravenous q day x 3 doses

• Initial corticosteroid dose
  – Prednisone (1mg/kg divided): Class IV or IV/V with crescents
  – Prednisone (0.5mg/kg): Class III, IV, or V without crescents

• Prednisone taper: after 4 weeks on full dose taper by 2.5mg every 2 weeks to 10mg/day by 6 months if no relapse
Induction Therapy for Class III/IV Lupus Nephritis Clinical Considerations (LOE: 3C)

- Cyclophosphamide vs mycophenolate mofetil are equivalent in most situations during first 6 months (LOE:1A).
  - Cyclophosphamide preferred (LOE:2B) for:
    - Poor prognostic factors: rapidly progressive renal deterioration (50% dec in creatinine from baseline) and/or cellular crescents/fibrinoid necrosis (esp > 25% of glomeruli)
    - Poor compliance

- Cyclophosphamide regimens:
  - NIH protocol (0.5-1.0 mg/m2 IV monthly x 6) (LOE:1B)
  - Euro-Lupus protocol (500mg IV q 2weeks x 6): best to give to Caucasian patients. Not tested in nonwhite races.
  - Other considerations: mesna, leuprolide

Induction Therapy for Class III/IV Lupus Nephritis
Clinical Considerations (LOE: 3C)

• Mycophenolate mofetil (MMF) and mycophenolic acid (MPA) dosing:

– Patients with LN Class V (pure membranous) and nephrotic range proteinuria should be treated with MMF and prednisone (0.5mg/kg/d with taper) for 6 months (LOE:2B).
  • In selected pts that are non-nephrotic and intolerant to MMF can consider azathioprine (LOE:4C)
– Patients with LN Class III/IV without adverse prognostic factors can be treated with MMF or CYC and prednisone (0.5mg/kg/day with taper) for 6 months (LOE:1A).
  • In selected pts that are intolerant to MMF and CYC can consider azathioprine (LOE:2C)

– All ethnicities with LN have similar responses to MMF
  • African-Americans and Hispanics may respond better to MMF than CYC

– Dose: MMF 2000-3000mg/day; MPA 1440-2160mg/day
  • Asians may respond to lower doses (MMF:2000mg/day) compared to other ethnicities that need higher dose.

Maintenance Therapy for Lupus Nephritis

• For patients who achieved complete or partial response at 6 months on CYC or MMF with taper of prednisone (\(\leq 10\) mg/d) (LOE:1A):
  – MMF: 1000-2000mg/d
  – Azathioprine: 2mg/kg/d. Best results in Caucasians. Consider if pregnancy planned.

• Continue maintenance therapy for at least 3 years (LOE:3C). Prednisone tapered to 5-7.5 mg/day by 12 months if possible.

Refractory Disease:  
Recommendations for Change in Therapy

- Patients who worsen within 3 months (> 50% increase in creatinine or proteinuria) or fail to respond (achieve partial remission) with 6 months of induction therapy should have change in therapy (LOE: 4C).
  - All pts should get 3 days of intravenous pulse methylprednisolone.
  - Pts on MMF could switch to CYC
  - Pts on CYC could switch to MMF
  - Pts who fail MMF or CYC can add or switch to rituximab or calcineurin inhibitors (especially Class V LN)
  - Belimumab being studied for induction and maintenance of certain presentations of LN.

Lupus Nephritis ACR Guidelines: Adjunctive Treatments

• All patients
  • Hydroxychloroquine
  • ACEi +/- ARBs >0.5 g/d proteinuria
  • BP <130/80
  • Statins: LDL >100 mg/dL
  • Calcium, vitD, D/C smoking, immunizations

• ASA and/or anticoagulation for mild thrombotic microangiopathy (TMA) on biopsy. If TMA predominant lesion treat with plasma exchange and anticoagulation.
  • Anticoagulation for nephrosis and albumin < 2.0gm/d

Pregnancy and Lupus Nephritis

- Pregnancy should be planned. Ideally LN (and lupus) should be inactive for 6 months with proteinuria < 1 gram/d and CrCl > 50ML/min.
  - Serum C3/C4 should rise during normal pregnancy
- Patients should be off MMF and CYC for 3 months before conception
- Hydroxychloroquine, prednisone, and azathioprine can be used during pregnancy. ASA to reduce preeclampsia risk.
- Blood pressure control without ACEi or ARBs. Can use labetalol or nifedipine.
- Close surveillance for postpartum flare of lupus and LN.

Systemic Lupus Erythematosus

- Belimumab is human monoclonal antibody that inhibits the soluble form of a B-cell survival factor (known as BLyS or BAFF).
- Belimumab approved in 2011 for active autoantibody-positive lupus (musculoskeletal or cutaneous disease that is unresponsive to standard therapy with glucocorticoids or other immunosuppressive agents).
  - Insufficient data: severe lupus nephritis: CNS disease
  - Reduced steroid use, improved fatigue
  - People with the highest disease activity (serological activity) had best response.
SLE and CVD Risk

• ‘SLE and RA may be unrecognized risk factors for women and have been associated with a significantly increased relative risk for CVD.

• Women with such conditions, but without clinically evident CVD should be considered at risk and screened for CVD risk factors.’

• ‘...women with prior CVD events should be screened for these conditions (SLE, RA) to allow for appropriate secondary prevention and to allow for the autoimmune condition to be addressed.’

Mosca et al., Circulation. 2011; 123:1243-62
Gout

• Prevalence of gout has doubled in last 30 yrs.
• 2008, prevalence increased to 8.3 million (3.9% pop) (1,2)
  – Males: 5.9% (6.1 million)
  – Females: 2.0% (2.2 million)
• Hyperuricemia affects 43.3 million (21%) adults (1)
• 3.9 million outpatient visits in 2002
  – ~70% to PCP and only 1.3% to rheumatologists

Kim Clin Ther. 2003;25:1593-617
### Comorbidities Associated With Gout & Hyperuricemia

<table>
<thead>
<tr>
<th>Comorbidity</th>
<th>Freq.</th>
<th>References</th>
</tr>
</thead>
</table>
Gout - Diagnosis

• SFA – Demonstration of MSU crystals

• DECT

• US – Double contour sign
Urate Crystals

Urate crystals in joint fluid neutrophils
(color-compensated polarized light microscopy)
DECT

GSI
Volume Rendering No cut

DFOV 41.3 x 28.2 cm
No Filter

Ex: Oct 26 2018
Gout – Urate deposit on hyaline cartilage
Gout 2012 ACR Guidelines – Part I

- Address education, diet, lifestyle & comorbidities.
- Allopurinol, febuxostat (**XOI**) are **1st line** Uric acid Lowering Therapies
- Decrease serum urate to improve signs & symptoms, with the **target** <6 mg/dl at a minimum.
- Rx allopurinol 100 qd & **titrate upward (even w/ CKD)**
- Test **HLA–B*5801** (PCR) in high risk pts [1]
- Combination ULT w/ uricosuric Rx may be needed
- **Pegloticase** is appropriate for patients with severe gout disease burden and refractoriness to, or intolerance of, appropriately dosed oral ULT options.

(1) Severe allopurinol hypersensitivity rxns (e.g., Koreans, Han Chinese and Thai populations)
Allopurinol Use with Renal Impairment

- **Allopurinol Package Insert**
  - “Allopurinol can substantially reduce uric acid in gout refractory pts, even in the presence of renal damage”
  - Some w/ pre-existing renal disease have shown a rise in BUN with allopurinol – monitor renal function early on
  - Renal failure only seen with neoplasia, myeloma, CHF
  - Pts with decreased renal function may require lower doses

- No mention of a ceiling dose for CRI
- Dose allopurinol according to effect, not renal function
  - If dosed to CrCl, hyperuricemia is not controlled

Bryant PrimHealthCare 2011;3:323
Stamp A&R 2011;63:412
Chao Curr Rheum Rep 2009;11:135
Dalbeth Rheum. 2006 33:1646
Gout 2012 ACR Guidelines – Part II

ACUTE GOUTY ARTHRITIS: Rx and Prophylaxis

- Initiate therapy within 24 hrs of acute attack
- **Continue ULT, w/o interruption, during acute flares**
- Use NSAIDs, corticosteroids, or oral colchicine 1st – line & combination therapy for severe or unresponsive pts
- PO colchicine or low-dose NSAIDs - when initiating ULT

Adjunctive Urate Lowering Drugs

- Calcium Channel blockers
- Losartan
- Fenofibrate
- Leflunomide
- Avoidance of unnecessary meds: diuretics, ASA

Gout Treatment

• When to start urate lowering therapy?
  – After a first attack, 40% of patients will experience another attack within the first year; 80% will experience a further attack within 2 years.

• British Society for Rheumatology Guidelines: Treat if risk for further attacks or damage by tophi is high

• EULAR guidelines: ULT indicated in patients with recurrent acute attacks, arthropathy, tophi, or radiographic changes

• ACR 2012 Guidelines: Treat when >1 attack/yr

Why Target Uric Acid < 6.0 mg/dl?

• 6 mg/dl (360 μmol/l) is below the saturation point of MSU (6.8 mg/dl)
  – <6.0 in most gout pts; 4-5 mg/dl in tophaceous pts
  – Prevent crystal formation; promote tophus dissolution

• Benefits of treat to target:
  – ↓frequency of attacks
  – ↓tophus volume
  – ↓urate crystal in synovial fluid
  – ↓Consequences of Gout, ↑sUA
# Pharmacotherapy for Gout

<table>
<thead>
<tr>
<th>Goal</th>
<th>Categories</th>
<th>Action</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperuricemia</td>
<td>Xanthine oxidase inhibitors</td>
<td>Prevents formation of uric acid</td>
<td>Allopurinol&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Febuxostat&lt;sup&gt;1&lt;/sup&gt;</td>
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<td></td>
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<td></td>
<td>Oxypurinol</td>
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<tr>
<td></td>
<td>Uricosuric agents</td>
<td>Increases excretion of uric acid</td>
<td>Probenecid&lt;sup&gt;1&lt;/sup&gt;</td>
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<td></td>
<td></td>
<td></td>
<td>Lesinurad</td>
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<td></td>
<td></td>
<td></td>
<td>*Sulfinpyrazone&lt;sup&gt;1&lt;/sup&gt;</td>
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<tr>
<td></td>
<td>Uricase</td>
<td>Uric acid → allantoin</td>
<td>Pegloticase&lt;sup&gt;5&lt;/sup&gt;</td>
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<tr>
<td></td>
<td></td>
<td>Urate dissolution</td>
<td></td>
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<tr>
<td>Acute attack</td>
<td>Anti-inflammatory</td>
<td>Reduce inflammation</td>
<td>NSAIDs&lt;sup&gt;1&lt;/sup&gt;</td>
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<tr>
<td></td>
<td></td>
<td>Manage acute attack</td>
<td>Colchicine&lt;sup&gt;1&lt;/sup&gt;</td>
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<tr>
<td></td>
<td></td>
<td>Use for prophylaxis</td>
<td>Steroids&lt;sup&gt;1&lt;/sup&gt;</td>
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<tr>
<td></td>
<td>Interleukin-1 inhibitors</td>
<td>Binds IL-1β or IL-1R</td>
<td>*Anakinra&lt;sup&gt;2&lt;/sup&gt;</td>
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<tr>
<td></td>
<td></td>
<td>Use for Prophylaxis</td>
<td>*Canakinumab&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>*Rilonacept&lt;sup&gt;4&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Gout - Facts

• <10% of Gout patient have crystal proven gout
• Anemia patients (10% population) 2x ↑ risk of gout
• Low dose ASA (81,325mg/d) ↑↑ gout attacks by 81% (RR 1.81). Effect nullified by Allopurinol use
• Allopurinol initiation during acute attacks is not associated with more/worse attacks/outcomes
• Cherries (+extract) consistently shown ↓ attacks
• CCB & losartan have ↓ risk of incident gout
• Gout patients have ↑ Cancer risk and ↓ risk Parkinson's
• RA found in 2-3.8% of gout pts

Febuxostat

- Selective xanthine oxidase inhibitor
- Phase II, III trials; doses of 40-80-120-240mg
- Use with renal insufficiency
  - metabolised by hepatobiliary conjugation
  - 60% (n=1673) treated with mild-moderate CRI (30-89 cc/min)
- Safe in pts with mild-mod hepatic dysfunction
- Can be safely given with colchicine, naproxen, indomethacin, hydrochlorothiazide or warfarin
- Increased mortality, CV & thromboembolic events
  - 1st eval (RCT/LTE): 9 Deaths FEB vs 0 Placebo
Lesinurad

- 90% of gout pts are underexcreters
- Lesinurad: oral inhibitor of URAT1, a transporter in the kidney that regulates uric acid excretion
- Lesinurad shown to be effective in:
  - allopurinol refractory gout
  - As adjunctive therapy (FBX or allopurinol)
- Activity of Lesinurad is not diminished in patients with varying degrees of renal impairment.

Pegloticase: Mechanism of Action

- Pegloticase is a pegylated modified porcine recombinant uricase
- FDA approval in 2010
- It converts uric acid to allantoin
  - Uric acid is sparingly soluble whereas allantoin is highly soluble
  - Allantoin is excreted efficiently by the kidneys

Pegloticase

• “most developed antibodies to pegloticase with adverse effects on safety and efficacy”
  –~90% tested positive for antibodies against (PEG) and the level of antibodies was correlated with infusion reaction ($P<0.001$)
  –Elevation of SUA > 6.0mg/dl surrogate for Abs and Rxns

• Eight serious cardiac adverse events in the pegloticase groups, including 2 sudden cardiac deaths, 2 exacerbations of congestive heart failure, 2 cases of dysrhythmia, 1 MI, and 1 case of angina. None in the control group

Pegloticase

• Dose: 8mg IV every 2 weeks
  – REQUIRED: Prophylaxis against infusion reactions
• Measure serum uric acid level prior to each infusion, consider d/c Rx if pre-treatment serum urate level > 6 mg/dL (esp. if this occurs > once)
• Other uric acid lowering drugs should be discontinued or not initiated prior to starting pegloticase.
• Safety Concerns:
  - G6PD deficiency
  - Infusion reactions/Anaphylaxis
  - CHF
  - Flares
Biologic for Gout

• Anakinra
• Canakinumab
• Rilonacept
Anakinra: Open Label reports of use in gout

- 10 pts OL Study - failed NSAID, colchicine, steroids
  - 100 mg x 3d: 10/10 responded to anakinra in 24-48 hours
- 24 hospitalized pts with acute gout + comorbidities Rx Anakinra
  19/22 dramatic improve by1d, 3/22 by d2
- 10 pts hospitalized -failed steroids. Rx anakinra x3d
  - 6 good response, 3 partial response
  - 9 pts w/ recurrent flares after d/c anakinra (ranging from
    3 to 45 days after)

2) Cho, et al ACR 2010 #163
3) Chen Semin Arthritis Rheum. 2010;40:210-4
Canakinumab: Mechanism of Action

• Human monoclonal anti-human IL-1β antibody
• Binds to human IL-1β and neutralizes its activity
• Reduces Flares with uric acid lowering treatment initiation
• Single dose Canakinumab or monthly x 4 superior to daily colchicine
• Canakinumab provides rapid pain relief in acute gout & significantly reduces the risk of recurrent flares compared with triamcinolone IM

1) Schlesinger N. Ann Rheum Dis. 2011 Jul;70(7):1264-71
Rilonacept: Mechanism of Action

• Rilonacept is a recombinant fusion protein with high affinity for IL-1β
• It also binds to IL-1α, and IL-1Ra
• Rilonacept reduces gout-induced inflammation by binding to IL-1β and blocking its interaction with the IL-1 receptor
• SURGE: RIL vs RIL/Indo vs Indomethacin alone
  – @ 3d: Indo superior to rilonacept in pain reduction
• 241 new allopurinol starts: PBO vs RIL
  – Pts:S UA 9, 4 attack/yr
  – Fewer ULT flares and dropouts w/ RIL

2) Gillespie J. *Journal of Inflammation Research.* 2010;3:1-8
4) Schumacher *Arthritis Care Res.* 2012 64:1462
Granulomatosis with Polyangiitis (GPA)  
(Formerly Wegener’s Granulomatosis)

• Affects ~3 in 100,000 persons  
  Male = female  
• Mean age of onset 41-65 years (can occur at any age)  
• Histologically - necrotizing granulomatous inflammation  
  vasculitis of small to medium vessels  
• Clinically Involvement of  
  – upper airways (~95% of Patients)  
  – lungs (~ 85% of Patients)  
  – kidneys (80% GN at some point, 20% have GN at  
    presentation)  
  can be rapidly progressive, lacks symptoms, proteinuria,  
  active urine sediment  
Histologically focal, segmental, crescentic, necrotizing GN, few to  
no immune complexes (pauci-immune)
Granulomatosis with Polyangiitis (GPA) (Formerly Wegener’s Granulomatosis)

- Ocular Involvement – 56% (Scleritis / episcleritis, orbital disease)
- Cutaneous Involvement – 46% of patients
- Neuropathy
Granulomatosis with Polyangiitis (GPA) Evaluation

• History: symptoms and duration
• Physical examination: nasal membranes, eye, skin, joint, nerve
• Radiographs: CXR even in the absence of symptoms
• Laboratories: CBC, CMP, ESR, Urinalysis, ANCA antibodies
Granulomatosis with Polyangiitis (GPA)

Methods of ANCA Testing

- Indirect Immunofluorescence: cANCA, pANCA
- ELISA (target antigen-specific): Proteinase 3, Myeloperoxidase
- GPA:
  - cANCA (75-90%)
  - pANCA (5-20%)
  - (-) ANCA up to 20%
Can (+) ANCA be used to diagnose GPA in place of a tissue biopsy?

- Depending on the clinical scenario and likelihood of disease
- Sinus, lung, renal disease: predictive value 90%
- Sinus and lung disease: predictive value of ANCA ~30-60% remains a high potential of infection/neoplasm
- (+) ANCA has poor positive predictive value in low prevalence populations
- Diagnosis by biopsy remains necessary in many instances
ANCA titers and disease activity

• ANCA titers modestly informative for disease activity
  - Most informative for individuals with renal involvement
• ANCA type is a prognostic indicator
  - PR3+ more likely to relapse
  - PR3+ more likely to respond to rituximab therapy (in post-hoc analysis)
• Following ANCA titers and CD19+ B cell counts can guide rituximab dosing for remission maintenance therapy (MAINRITSAN2)

Charles P et al. Ann Rheum Dis 2018
Goals of GPA treatment

- Save life: Untreated disease median survival was 5 months.

- Remission induction (Absence of disease)

- Relapse Prevention (Recurrence of disease activity after achieving remission)

- Minimize drug toxicity
GPA – Disease Severity

• SEVERE
  • Alveolar hemorrhage
  • Glomerulonephritis
  • CNS
  • Mononeuritis multiplex
  • Pericarditis
  • Vision threatening scleritis

  • TREAT with Cyclophosphamide or Rituximab

• NON SEVERE
  • Sinonasal disease
  • Oral mucosa
  • Skin
  • Conductive hearing loss
  • Musculoskeletal
  • Lung – no respiratory compromise

  • TREAT with Methotrexate
Cyclophosphamide vs Rituximab for Remission Induction (RAVE)

For remission induction, rituximab is as effective as cyclophosphamide (This was the basis for FDA approval of RTX for GPA/MPA in April 2011)

- 197 ANCA (+) GPA or MPA
  - Meeting primary end points:
    - All patients: RTX 64%, CYC 53% (p<0.001)
    - Relapsing patients:
      - RTX 67%
      - CYC 42%

- Rate of adverse events
  - RTX = CYC
  - Severe Relapse: RTX 6%, CYC 10%
  - Mortality rate: 2% (1 RTX, 2 CYC)
PEXIVAS Trial

• Plasma exchange does not reduce the risk of end-stage renal disease or death in patients with ANCA-associated vasculitis.

• Compared to a standard dose, reduced glucocorticoids did not substantially increase the risk of death or end-stage renal disease and resulted in fewer serious infections.

• The primary results of PEXIVAS, regarding both the use of plasma exchange and dosing of glucocorticoids, will have immediate and substantial impact on the standard of care for patients with ANCA-associated vasculitis.

EULAR recommendations for the use of imaging in large vessel vasculitis in clinical practice

• Recommendation 1:

• Suspected GCA: early imaging test to complement the clinical criteria for diagnosis (if high expertise and imaging modality is promptly available)

• Imaging should not delay initiation of treatment.

• If imaging modalities or expertise are not readily available, a biopsy should still be favored in first place.

• Imaging should be performed before or as early as possible after initiation of therapy, best within 1 week, because treatment with glucocorticoids rapidly reduces the sensitivity of imaging.
Recommendation 2:

In patients in whom there is a high clinical suspicion of GCA and a positive imaging test, the diagnosis of GCA may be made without an additional test (biopsy or further imaging). In patients with a low clinical probability and a negative imaging result, the diagnosis of GCA can be considered unlikely. In all other situations, additional efforts towards a diagnosis are necessary.
EULAR recommendations for the use of imaging in large vessel vasculitis in clinical practice

• Recommendation 3:

• Ultrasound of temporal ± axillary arteries is recommended as the first imaging modality in patients with suspected predominantly cranial GCA. A non-compressible ‘halo’ sign is the ultrasound finding most suggestive of GCA.

• Recommendation 4:

• High resolution MRI of cranial arteries to investigate mural inflammation may be used as an alternative for GCA diagnosis if ultrasound is not available or inconclusive.
EULAR recommendations for the use of imaging in large vessel vasculitis in clinical practice

• Recommendation 5:
• CT and PET are not recommended for the assessment of inflammation of cranial arteries.

• Recommendation 6:
• Ultrasound, PET, MRI and/or CT may be used for detection of mural inflammation and/or luminal changes in extracranial arteries to support the diagnosis of large vessel GCA.
Halo sign

A) Cross-sectional Doppler ultrasound view of the right temporal artery. The arrow shows the hypoechogenic halo sign.

B) Image 3 weeks after treatment, showing disappearance of the halo.

Ana Marina Suvelles, Enrique España-Gregori, José Tembl, Stephanie Rohrweck, Jose M. Millán, Manuel Díaz-López
Published 2010 in Clinical ophthalmology DOI:10.2147/OPTH.S13006
Treatment of GCA - Initial

• High dose Steroids
  • Non ischemic = Prednisone 1mg/kg, max 60 mg/day.
  • Ischemic = IV pulse methylprednisolone 500-1000 mg daily x 3 days followed by oral prednisone 1mg/kg, max 60 mg/day.

• Steroid dose reduction
  • 60 mg/day x 2 weeks, 50 mg/day x 2 weeks, then 40 mg daily.
  • Then reduce by 5 mg every 2 weeks till down to 20 mg/day.
  • Then reduce by 2.5 mg/day till down to 10 mg/day.
  • Then reduce even slower 1 or 2 or 2.5 mg every few weeks.
  • Duration of treatment 6-12 months.
Treatment of GCA - Subsequent

• Indications for steroid sparing drugs:
  • Significant premorbid disease (diabetes, osteoporosis, obesity)
  • Significant steroid side effects
  • Relapse

• Steroid sparing drugs:
  • Methotrexate (moderate efficacy)
  • Tocilizumab (rapid normalization of acute phase reactants)
Eosinophilic Granulomatosis with Polynagiitis (EGPA) Clinical and Labs

- Adult onset asthma, sinusitis, and other allergic manifestations
- Systemic vasculitis (including renal, skin)
  - Neurologic: ~70% with peripheral neuropathy (mononeuritis multiplex, distal symmetric polyneuropathy)
  - Cardiac: eosinophilic myocarditis/pericarditis, eosinophilic vasculitis (including coronary arteritis)
    - Cause of mortality in 50% of patients
    - More common in ANCA negative
    - Echocardiogram, cardiac MRI, troponin I
- Peripheral and tissue eosinophilia
  - Generally >1500 and >10% of WBC, steroid responsive
- ANCA+ (generally p-ANCA/MPO) only in 40%; prognostic value
Eosinophilic Granulomatosis with Polynagiitis (EGPA) 

Treatment

• Asthma: inhaled beta-agonists/corticosteroids
• Sinusitis: non-systemic therapy, e.g., nasal rinses, intranasal steroids
• Systemic disease: dependent on disease severity
  - Glucocorticoids: > 80% require daily low dose prednisone (< 10 mg/day)
  - Life-threatening/organ-threatening disease
    • Cyclophosphamide: po (2 mg/kg/day) or IV (CYCLOPS regimen)
    • Rituximab (2nd line): case series (n=41) with varying RTX regimens
      - 6 months: 34% complete response, 49% partial response
      - 12 months: 49% complete response, 39% partial response
      - Higher response rate if ANCA +
Mepolizumab in EGPA

• IL-5: responsible for the maturation, activation and survival of eosinophils
• Mepolizumab is a Monoclonal antibody directed against of IL-5. Prevents binding of IL-5 to receptor on eosinophils

• FDA approved for:
  • severe eosinophilic asthma as add-on therapy; November 2015
  • EGPA; December 2017 (300 mg subQ every month)