Pharmacological Management of Rheumatoid Arthritis
Therapeutic Options

Pharmacologic

• Control inflammation and pain with NSAIDS (limited effect)
• Control pain with analgesics i.e. acetaminophen, opioids
• Suppress disease activity with DMARDs
• Consider biologic therapy
Therapeutic Approaches

• Include early use of single or combination of traditional disease modifying anti-rheumatic drugs (DMARDS)
• NSAIDs
• Low dose prednisone
• Biologic Response Modifiers
Conventional Use of DMARDs in the Treatment of RA

Early mild disease
- Hydroxychloroquine 200 mg daily or bid (up to 6.5 mg/kg/d)
- Sulfasalazine start with 500 mg once daily and inc to 2-3 g daily in 2 divided doses

Active disease or with indication of poorer prognosis:
- Methotrexate weekly with Folic Acid
  - 7.5-25 mg once weekly, up to 20-25 mg/wk more effective than low doses
  - In early RA as effective as etanercept in slowing radiographic disease progression over 1 year
  - Decreases overall risk for mortality and CV death
Conventional DMARDs

Combination therapy with Methotrexate: Sulfasalazine, Hydroxychloroquine in *early RA* (Dx within 3 months)

- greater efficacy, remission rate, and less radiologic progression than monotherapy

Combination Therapy in *established RA*

- Response enhanced by triple > double therapy
- Best combination regimen still unknown
Better outcome with early treatment

Estimated Proportion Achieving Remission (%)

Early Late (> 4 months) P=0.010

Mottonen et al Arthritis and Rheumatism 2002
## Monitoring DMARDs

### ALL DMARDs:
- Baseline CBC, Cr, LFTs
- Update pneumococcal and influenza vaccinations

<table>
<thead>
<tr>
<th>Drug</th>
<th>Parameter</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydroxychloroquine</td>
<td>Eye exam q 12 months</td>
</tr>
<tr>
<td>Sulfasalazine</td>
<td>CBC and LFTs at 1 month then q 3 months</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>CBC, Cr, LFTs q 1-3 months, CXR</td>
</tr>
<tr>
<td>Leflunomide - ARAVA®</td>
<td>CBC, Cr, LFTs, blood pressure q 1 month x 6 months, then q 3 months</td>
</tr>
</tbody>
</table>
Monitoring DMARDs

Indications to hold DMARDs:

- LFTs $> 3 \times$ upper limit of normal
- Methotrexate, leflunomide,
  - WBC $< 3$
  - Platelets $< 50$
- Contact the Rheumatologist!
Biologic Response Modifiers

- Etanercept - Enbrel®
- Infliximab - Remicade®
- Adalimumab - Humira®
- Golimumab - Symponi®
- Abatacept – Ocrevus® (T-cell inhibitor)
- Rituximab – Rituxan® (B-cell inhibitor)
- Tocilizumab - Actemra® (IL-6 receptor inhibitor)

TNFα antagonists
Biologic Response Modifiers: Special Monitoring

Baseline:
• CXR, TB skin test, HIV screen, (histoplasmosis, coccidiomycosis);
• update immunizations, e.g. flu shots, pneumococcal vaccine

Ongoing: close clinical follow-up to avert infections
• In the case of infection requiring antibiotics, biologic agent needs to be ‘held’ until infection has resolved
• Hold 1 week pre and post op, due to infection risk
## Yearly Cost $CDN

<table>
<thead>
<tr>
<th>Drug</th>
<th>Onset</th>
<th>Yearly Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydroxychloroquine</td>
<td>2-6 months</td>
<td>$190</td>
</tr>
<tr>
<td>Sulfasalazine</td>
<td>1-3 months</td>
<td>$615</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>1-2 months</td>
<td>$260 po/325inj</td>
</tr>
<tr>
<td>Leflunomide</td>
<td>1-4 months</td>
<td>$1750</td>
</tr>
</tbody>
</table>
## Yearly Cost $CDN

<table>
<thead>
<tr>
<th>Drug</th>
<th>Onset</th>
<th>Yearly Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triple</td>
<td>1-6 months</td>
<td>1,124</td>
</tr>
<tr>
<td>Anakinra</td>
<td>3 months</td>
<td>~20,000</td>
</tr>
<tr>
<td>Etanercept</td>
<td>1-3 months</td>
<td>~20,000</td>
</tr>
<tr>
<td>Infliximab</td>
<td>1-4 months</td>
<td>~12,000</td>
</tr>
<tr>
<td>Adalimumumab</td>
<td>1-3 months</td>
<td>~20,000</td>
</tr>
</tbody>
</table>
Cardiovascular risk in RA patients

• Increased incidence of cardiovascular events eg. AMI and sudden cardiac death in RA patients.

• Likely mediated by both traditional risk factors and factors unique to RA (eg. chronic inflammatory state, sedentary lifestyle) and management (eg. steroids, NSAIDs).

• Cardiovascular events appear one decade earlier in RA patients than controls.
Cardiovascular risk in RA patients

- RA patients are more likely to have clinically silent CAD and more likely to have unrecognized myocardial infarction and sudden cardiac death.

- Recurrent ischemic events occur more frequently after acute coronary syndrome in RA patients.

- RA (especially RF positive) patients are at a significantly higher risk of congestive heart failure and higher risk of death related to CHF.
Guidelines for CV risk management

Many unanswered questions, but….

1) Yearly CV risk assessment for patients >50.
2) Encourage smoking cessation.
3) Limit use of NSAIDs and glucocorticoids.
4) Controlling underlying disease may improve risk. Not sure yet.
5) Discourage sedentary lifestyle.
6) CVD risk scores should be increased by a factor of 1.5 in patients with RA, esp. if long standing disease, seropositive and extra-articular manifestations.
Summary: Pharmacological Management of RA

• Patient education
• Early aggressive therapy yields better patient outcome
• Combination DMARD therapy is state of the art
• Biologic Response Modifiers may be added to baseline therapy
• Monitor for drug side effects