Rheumatoid Arthritis
Early Diagnosis and Treatment

Speaker Name: Dr. Milton Baker
Date: June, 2017
Disclosure Slide

Have been Principle Investigator in numerous Clinical Trials. These have been phase 2, 3 and 4 trials. Sponsored by Janssen, Abbvie, Celgene, UCB, Pfizer, Eli Lilly, Roche, BMS and others.

Also have been at numerous Adboards, sponsored by the same companies.

I have no significant investments in any of these companies.
Program Outline

Diagnosis and Referral

- Canadian inflammatory arthritis landscape
- Identifying inflammatory arthritis
- Evaluation & differential diagnosis of RA
- Referral considerations

Therapeutic Management

- Fundamental concepts
- Treatment algorithm
- Therapeutic options
- Treatment assessment

The PCP’s Role in Ongoing Management

- Vaccination
- Pregnancy
- Intercurrent infections
- Malignancy
- Surgery
Diagnosis and Referral
Existing therapies and their limitations: DMARDs

Goals: improve symptoms and delay disease progression (occasionally cause remission)

Use as early as possible (onset of action 1–6 months)

Limitations

- Requires assessment of a rheumatologist
- More than 1 drug may be required
- Side effects, e.g., myelosuppression, rash, GI intolerance
- May not have lasting efficacy

Goals: treatment of symptomatic joints, recovery of motion

Useful in bridging for the DMARD effect

Limitations

- Temporary benefit/not advisable for long-term therapy
- Local injections/systemic disease
- Inappropriate as only treatment
- Side effects, e.g., osteoporosis, hypertension, hyperglycemia, cataracts, weight gain, hyperlipidemia
- Increased risk of infection

Existing therapies and their limitations: NSAIDs

Goals: relief of joint pain and swelling

Analgesic effects immediate, 2–3 weeks for optimal reduction in inflammation

Limitations

- Ineffective as sole therapy for RA
- Do not prevent joint damage
- Side effects, e.g., dyspepsia (common), gastric bleeding, renal insufficiency
- Drug interactions

Criteria for classification of rheumatoid arthritis

4/7 criteria for RA diagnosis (present for \( \geq 6 \) weeks):

1. Morning stiffness lasting \( \geq 1 \) hour
2. Simultaneous arthritis of \( \geq 3 \) joints
3. Arthritis of hand joints
4. Symmetrical arthritis
5. Rheumatoid nodules
6. Abnormal serum rheumatoid factor
7. Radiographic changes typical of RA on posteroanterior hand and wrist radiographs

Rheumatoid arthritis is a systemic disease

Symmetrical polyarthritis

Prolonged morning stiffness (>45 min)

Extra-articular manifestations

Constitutional features (weight loss, fatigue)
Rising Prevalence of RA in Canada

By 2040, an estimated 549,218 Canadians (1.3% of the Canadian population) will be living with RA.

Arthritis Alliance of Canada. Fall, 2011; available at www.arthritisalliance.ca.
What questions would you ask your patients in order to make the distinction?

Do you find it difficult to distinguish mechanical from inflammatory arthritis?
Ask the Right Questions to Distinguish Mechanical from Inflammatory Pain

Key questions:

- Where exactly does it hurt and for how long?
- When does it hurt most (i.e., with activity, at rest, both)?
- Do you suffer from pain accompanied by morning stiffness lasting for more than 30 minutes?
- Has the pain (with the exception of knee pain) woken you at night for more than 6 weeks?
- Is pain improved upon movement? What are some other aggravating/relieving factors?

Steering committee, personal communication, September 2014.
Discriminating Inflammatory from Non-inflammatory Joint Pain

Use clues from the patient’s history and exam to generate a differential diagnosis:

<table>
<thead>
<tr>
<th>Feature</th>
<th>Inflammatory</th>
<th>Non-inflammatory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Joint pain</td>
<td>Usually improves with activity</td>
<td>Usually worsens with activity</td>
</tr>
<tr>
<td>Joint swelling</td>
<td>Soft tissue</td>
<td>Bony</td>
</tr>
<tr>
<td>Joint deformity</td>
<td>Common</td>
<td>Common</td>
</tr>
<tr>
<td>Local erythema</td>
<td>Sometimes</td>
<td>Absent</td>
</tr>
<tr>
<td>Local warmth</td>
<td>Frequent</td>
<td>Absent</td>
</tr>
<tr>
<td>Morning stiffness</td>
<td>&gt; 30 minutes</td>
<td>&lt; 30 minutes</td>
</tr>
<tr>
<td>Systemic symptoms</td>
<td>Common, especially fatigue</td>
<td>Absent</td>
</tr>
</tbody>
</table>

Some signs may be suppressed by NSAIDs

Patterns of Joint Involvement

What does each of these images indicate? Why?

Early RA

Late RA

Osteoarthritis

Psoriatic arthritis

Figures courtesy of Dr. H.L. Averns. Reprinted with permission.
Clinical suspicion of RA is supported by the presence of ANY of the following:

- ≥ 3 swollen joints
- MTP/MCP involvement
  - Positive squeeze test
- Morning stiffness ≥ 30 mins

### Inflammatory Features Suggesting Diagnosis Other than RA

<table>
<thead>
<tr>
<th>System</th>
<th>Feature</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td>• Mucosal ulcers</td>
</tr>
<tr>
<td></td>
<td>• Photosensitivity</td>
</tr>
<tr>
<td></td>
<td>• Psoriasis</td>
</tr>
<tr>
<td></td>
<td>• Skin rashes</td>
</tr>
<tr>
<td>Eye</td>
<td>• Uveitis</td>
</tr>
<tr>
<td>Bowel</td>
<td>• Inflammatory bowel disease</td>
</tr>
<tr>
<td></td>
<td>• Infectious diarrhea</td>
</tr>
<tr>
<td>Other</td>
<td>• Raynaud’s</td>
</tr>
<tr>
<td></td>
<td>• Urethritis</td>
</tr>
<tr>
<td></td>
<td>• Self-limiting post-viral symptoms</td>
</tr>
</tbody>
</table>

# Diagnostic Laboratory and Imaging Tests

Recommended for initial evaluation of RA

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP</td>
<td>Often increased</td>
</tr>
<tr>
<td>ESR</td>
<td>Often increased to &gt; 30 mm/hr</td>
</tr>
<tr>
<td>Hemoglobin/hematocrit</td>
<td>May be decreased</td>
</tr>
<tr>
<td>Liver function</td>
<td>Normal or slightly elevated alkaline phosphatase</td>
</tr>
<tr>
<td>Platelets</td>
<td>Usually increased</td>
</tr>
<tr>
<td>WBC</td>
<td>May be increased</td>
</tr>
<tr>
<td>Radiographic findings of involved joints</td>
<td>May be normal or show osteopenia or erosions near joint spaces in early disease</td>
</tr>
</tbody>
</table>

**Auto-antibodies: RF and Anti-CCP**

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity(^1) (% of RA patients who are positive)</th>
<th>Specificity(^1) (% of non-RA patients who are negative)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RF</td>
<td>~60-65%</td>
<td>~80%</td>
</tr>
<tr>
<td>Anti-CCP</td>
<td>~68%</td>
<td>~95%</td>
</tr>
</tbody>
</table>

- Even when these tests are negative, the patient may still have RA\(^1\)
- Anti-CCP is highly specific for RA, but may also be found in other types of inflammatory arthritis\(^2\)
- Both RF and anti-CCP seropositivity are associated with more severe disease\(^2\)

Do you feel Lost?
When should a patient be referred to a rheumatologist?

Why is referral important?
Brief Delay of Therapy Affects Radiographic Outcomes

Important Considerations for Referral

- > 12 weeks delay in treatment results in a missed opportunity to improve long-term outcomes\(^1\)
- RF positivity, raised acute phase response, and erosions on x-ray are associated with poor outcomes\(^1\)
  - Their absence at presentation should not preclude diagnosis or referral\(^1\)
- Ongoing/untreated systemic inflammation is associated with increased comorbidities (cardiovascular disease, cancer) in patients with RA\(^2,3\)
- Corticosteroids should generally be avoided without a confirmed diagnosis of RA\(^1\)

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Early Referral May Improve Outcomes

Active synovitis can lead to cartilage and bone destruction and the rapid onset of functional disability\(^1\)

Early treatment is associated with:

- A 33% reduction in radiographic damage\(^2\)
- An approximately 2-fold increase in disease remission\(^3\)

Referral to a rheumatologist:

- Is supported by CRA and international guidelines\(^1,4\)
- Results in improved outcomes\(^5\)


Figure courtesy of Dr. H.L. Averns. Reprinted with permission.
Referral Information Needed by Rheumatologist

- Reason for consultation
- Duration of symptoms
- Duration of morning stiffness
- Limitation of daily/work activities
- Involved joints
- Laboratory tests
  - RF
  - CRP
  - ESR

Summary

- Ask the right questions in order to distinguish mechanical from inflammatory pain
- Use clues from the history and physical exam for differential diagnosis
  - Laboratory and imaging studies can be helpful, but often a diagnosis can be made on the basis of history and physical exam alone
- Rule out inflammatory features suggesting diagnoses other than RA
- If RA is suspected or diagnosed, early referral to a rheumatologist may lead to improved long-term outcomes
Therapeutic Management
Therapeutic Management – Learning Objectives

Following this section of the talk, participants should be able to:

- Appreciate the fundamental concepts that guide RA treatment
- Specify the key components of the CRA RA treatment algorithm
- Evaluate appropriate usage of glucocorticoids
- Differentiate biologic and non-biologic DMARDs used to treat RA
- Describe common measures of disease activity
Your patient has significant joint involvement and you suspect RA; however, she is reluctant to see a rheumatologist.

What would you say to her?
Goals: improve symptoms and delay disease progression (occasionally cause remission)

Use as early as possible (onset of action 1–6 months)

Limitations:

- Requires assessment of a rheumatologist
- More than 1 drug may be required
- Side effects, e.g., myelosuppression, rash, GI intolerance
- May not have lasting efficacy

Existing therapies and their limitations: DMARDs

Management of RA: Fundamental Concept

Tight control of inflammation improves outcomes and requires structured protocols and regular review.

Inflammation (disease activity) → Joint damage → Disability

Figure reproduced from Smolen JS et al. *Ann Rheum Dis* 2009;68:159-62.
CRA Guidelines: Initial Treatment of RA

- **Diagnosis of RA**
- **Aim for goal of remission** (or LDA when not possible)
- **Assess disease activity and prognostic features**
- **Start DMARD as soon as possible**

### DMARD monotherapy: MTX unless CI
- **Inadequate response**
  - **Switch DMARD**

### DMARD combination therapy: with MTX unless CI
- **Inadequate response**
  - **Proceed to biologic therapy**

**Inadequate response = not reaching target by 3 to 6 months**

**In certain situations:**
1. DMARD CI
2. HDA + poor prognostic factors (esp early disease)

Is it ever reasonable to prescribe steroids?
Glucocorticoids

- Glucocorticoids (oral, intramuscular, or intra-articular) can be added to DMARD therapy as part of the initial treatment strategy and may be an option for
  - Managing flares
  - Bridge therapy while waiting for DMARD therapy to take effect
  - Symptom control if no other options exist

- Glucocorticoids should be used in the lowest possible dose and tapered as soon as clinically possible

Conquering the Step-Care Pyramid

1. Onset of Rheumatoid Arthritis
2. Family Physician
3. Rheumatologist
4. DMARDs
5. Control
The Momentum/Consequences of RA

Disease Temperament x Time = ↑ Joint Damage
Choose your poison
Leading DMARDs, Low Toxicity

<table>
<thead>
<tr>
<th>Drug</th>
<th>Standardized Toxicity Index</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methotrexate</td>
<td>3.82 ± 0.35</td>
</tr>
<tr>
<td>Hydroxychloroquine</td>
<td>1.38 ± 0.15</td>
</tr>
<tr>
<td>IM Gold</td>
<td>2.27 ± 0.17</td>
</tr>
</tbody>
</table>
Non-biologic DMARDs

Most commonly used DMARDs

- Methotrexate
- Sulfasalazine (Salazopyrin®)
- Hydroxychloroquine (Plaquenil®)
- Leflunomide (Arava®)
- Azothiaprine
- Gold (Myochrisine®)

Double and triple combinations regimens are also available

Roughly 2/3 of patients initially respond to non-biologic DMARD monotherapy (approximately 60% reduction in pain, swelling and stiffness)

Combination DMARDs may offer an advantage for some patients

## Non-biologic DMARDs

<table>
<thead>
<tr>
<th>PRODUCT</th>
<th>Dose</th>
<th>Time to onset</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methotrexate (po or sc)</td>
<td>Up to 25 mg per week</td>
<td>4 to 6 weeks</td>
</tr>
<tr>
<td>Hydroxychloroquine</td>
<td>200 to 400 mg QD</td>
<td>4 to 12 weeks</td>
</tr>
<tr>
<td>Sulfasalazine</td>
<td>1 g BID to QID</td>
<td>5 to 10 weeks</td>
</tr>
<tr>
<td>Leflunomide</td>
<td>10 to 20 mg daily</td>
<td>4 to 12 weeks</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>2.5 to 5 mg/kg/d 2 intakes</td>
<td>6 to 12 weeks</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>50 to 150 mg QD</td>
<td>6 to 12 weeks</td>
</tr>
<tr>
<td>Gold salts (i.m.)</td>
<td>25-50 mg q2-4 weeks</td>
<td>3 to 6 months</td>
</tr>
<tr>
<td>Tofacitinib</td>
<td>5 mg twice daily</td>
<td>2 to 12 weeks</td>
</tr>
</tbody>
</table>
Research-Supported Combination DMARDs

Double Combinations

- methotrexate + hydroxychloroquine
- methotrexate + cyclosporin A
- IM gold + cyclosporin A
- IM gold + hydroxychloroquine

Triple Combinations

- Hydroxychloroquine + methotrexate + cyclophosphamide
- Hydroxychloroquine + methotrexate + azathioprine
### Arava

<table>
<thead>
<tr>
<th>Inhibits de novo pyrimidine synthesis</th>
</tr>
</thead>
<tbody>
<tr>
<td>▶ Inhibits DHODH (dihydroorotate dehydrogenase), an enzyme required for the de novo synthesis of pyrimidines</td>
</tr>
<tr>
<td>▶ Prevents mitogen-stimulated T cells from entering the S phase of the cell cycle</td>
</tr>
<tr>
<td>▶ Limits the proliferation of both in vivo and in vitro activated lymphocytes</td>
</tr>
</tbody>
</table>

### Methotrexate

<table>
<thead>
<tr>
<th>Inhibits purine synthesis</th>
</tr>
</thead>
<tbody>
<tr>
<td>▶ Interferes with the production of cytokines that promote inflammation, specifically IL-1, TNF-α, IL-6, and IL-8</td>
</tr>
<tr>
<td>▶ Enhances the production of cytokines that have anti-inflammatory properties, specifically IL-10</td>
</tr>
<tr>
<td>▶ Promotes the buildup of adenosine—a potent anti-inflammatory agent—in the extracellular space where it can prevent accumulation of neutrophils</td>
</tr>
</tbody>
</table>
Leflunomide- Adverse effects

Diarrhea, nausea, dyspepsia 10-20%

Headache 11%

Rash 11%

Elevated Liver Function Tests 14%

Serious Adverse Effects- 104,000 Pt. Years

129 Serious Liver- 15 cases of Liver failure, 2 cases of Liver cirrhosis.
Arava blocks clonal expansion of rapidly proliferating cells by inhibiting pyrimidine synthesis

Resting T Cell

$G_0 \rightarrow G_1 \rightarrow S$
Arava- Leflunomide

Figure 1. Rate of ACR Success at Endpoint for Placebo-Controlled Pivotal Trials

- US 301 (52 wks)
- MN 301 (24 wks)
- MN 301/303 (48 wks)

Percentage

LEF  | PL  | MTX |
----  |----  |-----|
40    |     |     |
35    |     |     |
30    |     |     |
25    |     |     |
20    |     |     |
15    |     |     |
10    |     |     |
5     |     |     |
0     |     |     |

LEF  | PL  | SSZ |
----  |----  |-----|
40    |     |     |
35    |     |     |
30    |     |     |
25    |     |     |
20    |     |     |
15    |     |     |
10    |     |     |
5     |     |     |
0     |     |     |

LEF  | SSZ |
----  |-----|
40    |     |
35    |     |
30    |     |
25    |     |
20    |     |
15    |     |
10    |     |
5     |     |
0     |     |

* Significant difference
+ Trend
Biologics are large, complex proteins grown through biological processes using living cells (from mice, humans, or microorganisms).

They reduce inflammation by blocking key molecules involved in the pathogenesis of RA.

### Available TNF Inhibitors

<table>
<thead>
<tr>
<th>Subcutaneous (SC)*</th>
<th>Injection/Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adalimumab (Humira)</td>
<td>Every 2 weeks</td>
</tr>
<tr>
<td>Certolizumab (Cimzia)</td>
<td>3 injections in the first month, then every 2 or 4 weeks</td>
</tr>
<tr>
<td>Etanercept (Enbrel)</td>
<td>Once or twice a week</td>
</tr>
<tr>
<td>Golimumab (Simponi)</td>
<td>Once a month</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Intravenous (IV)</th>
<th>Infusion/Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infliximab (Remicade)</td>
<td>Infusion done initially, week 2 and 6, then every 6 to 8 weeks</td>
</tr>
</tbody>
</table>

*Injection into thigh or stomach (body fat)*
## Biologic Options for RA

<table>
<thead>
<tr>
<th>Mechanism of action</th>
<th>Name</th>
<th>Trade name</th>
<th>Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Inhibits tumour necrosis factor</strong></td>
<td>Adalimumab&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Humira</td>
<td>SC</td>
</tr>
<tr>
<td></td>
<td>Certolizumab pegol&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Cimzia</td>
<td>SC</td>
</tr>
<tr>
<td></td>
<td>Etanercept&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Enbrel</td>
<td>SC</td>
</tr>
<tr>
<td></td>
<td>Golimumab&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Simponi</td>
<td>SC</td>
</tr>
<tr>
<td></td>
<td>Golimumab&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Simponi IV</td>
<td>IV</td>
</tr>
<tr>
<td></td>
<td>Infliximab&lt;sup&gt;1,2&lt;/sup&gt;</td>
<td>Remicade Inflectra</td>
<td>IV</td>
</tr>
<tr>
<td><strong>Inhibits interleukin-6</strong></td>
<td>Tocilizumab&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Actemra</td>
<td>IV</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>SC</td>
</tr>
<tr>
<td><strong>Inhibits interleukin-1</strong></td>
<td>Anakinra</td>
<td>Kineret</td>
<td>SC</td>
</tr>
<tr>
<td><strong>Inhibits T cell activation</strong></td>
<td>Abatacept&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Ocrevus</td>
<td>IV</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>SC</td>
</tr>
<tr>
<td><strong>Depletes B cells</strong></td>
<td>Rituximab&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Rituxan</td>
<td>IV</td>
</tr>
</tbody>
</table>

Full reference list provided in the slide notes.

*Maintenance frequency except for rituximab
Biologics: Possible Side Effects

*Increased risk of infection*
*Colds or sinus infections*
*Injection site reactions*
*Infusion reactions*
*Headaches/dizziness*
*Nausea or diarrhea*

- Reactivation of infections like hepatitis or tuberculosis
- Risk of skin cancer
Evaluating Disease Activity: Functional and Joint Assessments

**HAQ-DI**

- Patient-reported assessment of function
  - 20 questions on activities of daily living
  - 13 questions on use of assistive devices
  - 8 questions on receiving help from others
- Scored from 0 (no functional impairment) to 3 (complete impairment)

**Tender and Swollen Joint Counts**

- Based on 16 to 68 joints; 28 is most common

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Summary

- Minimizing cumulative inflammation has the potential to reduce or prevent joint damage and disability
- Once RA is confirmed, the CRA recommends starting DMARD therapy as early as possible
  - Many biologic and non-biologic DMARDs are currently available
  - DMARD therapy should be switched if response is inadequate
  - Glucocorticoids should be used sparingly and only under specific circumstances
- The goal of treatment is remission
- Several outcome measures are available to monitor disease activity
The PCP’s Role in Ongoing Management
The PCP’s Role in Ongoing Management – Learning Objectives

Following this section of the talk, participants should be able to:

- List vaccinations required by RA patients before and during immunosuppressive therapy
- Recognize the importance of careful pregnancy planning and management in women with RA
- Manage infections in patients with RA on immunosuppressive therapy
- Assess the need for perioperative management of drug therapy in patients with RA
Final Thoughts

- Ask the right questions to distinguish mechanical from inflammatory pain
- If RA is suspected or diagnosed, early referral to a rheumatologist may lead to improved outcomes
- Goal of treatment is to minimize cumulative inflammation to reduce/prevent joint damage and disability
- DMARD therapy is recommended as early as possible following RA diagnosis
- The PCP plays a vital role in ongoing management of RA patients, particularly with regard to vaccination optimization, pregnancy planning, intercurrent infections, and peri/post-operative management
CRA Guidelines: Goals and Baseline Assessments

- The goal of treatment is remission and, when not possible, minimal disease activity while
  - Controlling symptoms
  - Halting damage
  - Preventing disability
  - Improving quality of life

- Poor prognostic features should be assessed at baseline and considered when making treatment decisions
  - Lab assessments: RF+, anti-CCP+, high ESR/CRP
  - Other assessments: functional limitation, high SJC/TJC, early erosions, extra-articular features
