Treatment Options for Managing Rheumatoid Arthritis

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Conflict of Interest Disclosure

Disclosure

I do not have any financial relationships to disclose.
Objectives

- Explain the mechanisms of action for DAMRDS.
- Discuss the major ADRs related to DAMRDS.
- Explain PD and PK of most commonly used DAMRDS.
Early Arthritis- case scenario

- 55 YOF complains of months of bilateral hand pain. She describes progressive morning stiffness lasting 3 hours with wrist and MCP pain and swelling.
- She has also noted some discomfort and perhaps swelling in her wrists, shoulders, knees, and toes. Review of systems is unremarkable
- PMHx: GERD, PUD
- Family History: adopted, No Etoh or other drugs
- Labs: CBC normal, elevated Scr (1.7 mg/dl) RF positive

- A/P: Pt was given high dose NSAIDs with some improvement and referred to Rheumatology
Early Arthritis- case scenario

- 42 y/o Caucasian woman with bilateral hand and wrist pain x 3 months
- ROS: + morning stiffness x 45-60 minutes, + fatigue
- Family History: + RA (mother and maternal aunt)
- Social Hx: + tobacco
- PE: synovitis over right 2\textsuperscript{nd} and 3\textsuperscript{rd} MCPs and right wrist
- Labs: CBC with mild normo/normo anemia; RF and ANA negative x 2; CRP 2.3
- Hand XRAY-s: no abnormalities

- A/P: Pt was given small dose Prednisone with mild improvement and referred to Rheumatology
Therapy - current choices

• NSAIDs
• “disease-modifying” anti-rheumatic drugs
• corticosteroids
• “biologic agents”
• no “cure”, only “control”
• limitations
Disease-Modifying Antirheumatic Drugs (DMARDs)
<table>
<thead>
<tr>
<th>Drug</th>
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Traditional Treatment Pyramid

BASED ON 3 ASSUMPTIONS

1. RA = Benign - Non-life threatening disease

2. Aspirin and NSAID are benign drugs

3. DMARD’s are too toxic
Therapeutic wheel of fortune?
Reduction of Joint Damage

Disease-modifying Anti-Rheumatic Drugs (DMARDs)
- Methotrexate
- Sulfasalazine
- Leflunomide
- Hydroxychloroquine
- Azathioprine
- Cyclosporine
- Gold
- Penicillamine

Biologic drugs
- Anti-TNF therapy:
  - Infliximab
  - Etanercept
  - Adalimumab
  - Certolizumab
  - Golimumab
- Rituximab
- Abatacept
- Tocilizumab
RA - choosing a remittive agent

Mild RA
- hydroxychloroquine
- sulfasalazine

Moderate RA
- hydroxychloroquine
- sulfasalazine
- methotrexate

Severe RA
- methotrexate
- azathioprine
- leflunomide
- biologic modifiers
- combinations
Case presentation - therapy

- NSAID
- low dose prednisone
- methotrexate
- biologic

- weeks 0-3
- weeks 4-16
- weeks 17+
Disease-Modifying Antirheumatic Drugs (DMARDs)
Methotrexate

Tetrahydrofolate is an important cofactor in the production of purines transferring a carbon atom.
Methotrexate

• **Dose and Administration**
  – Dose ranges from 7.5 to 25 mg
  – **ONLY GIVEN ONCE A WEEK**
  – 2.5 mg Tablets or Subcutaneous Injection 25 mg/mL

• **Onset of Action**
  – 6-8 weeks

• **Avoid**
  – Pregnancy – Teratogenic
  – Alcohol
  – Sulfa Antibiotics
  – NSAIDs
Methotrexate

• **Common S/E**
  – Malaise, Nausea
  – Rise in Liver Enzymes

• **Dose/Sensitivity**
  – Oral ulcers, alopecia, liver and bone marrow toxicity

• **Rare S/E**
  – Pulmonary: Fever, cough, SOB (early, old, lung disease)
  – Bone Marrow: Follow bloodwork – dose/sensitivity related
  – Infection
  – Pregnancy
  – Malignancy
MTX- Monitoring

- Folic Acid supplementation may help with side effects
- 1 mg daily or 5 mg weekly

What labs are ordered to monitor for safety?
- CBC (q 4-8 weeks)
- Transaminases, albumin (q 4-8 weeks)
- Creatinine (renal function)
Hydroxychloroquine (Plaquenil®)

• Anti-malarial medication found useful for the treatment of inflammatory arthritis
• Highly concentrated within cells
• Increases intracellular pH
• Interferes with cell’s ability to degrade and process proteins
Hydroxychloroquine (Plaquenil®)

- **Dose & Administration**
  - 200 mg tablets
  - Dose ranges from 200 – 400 mg per day

- **Onset**
  - 6-12 weeks

- **Avoid**
  - May increase sensitivity to the sun
Hydroxychloroquine (Plaquenil®)

• Common S/E
  – Rash, nausea, diarrhea
  – Difficult with reading (affects accommodation)

• Rare S/E
  – Ocular, Skeletal muscle, heart
Hydroxychloroquine Monitoring

• Dose is based on lean body weight (6.5 mg/kg/day)
• Average Dose 200-400 mg BID
• Ophthalmologic screen for visual acuity, colour vision, and visual fields qyearly
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Leflunomide (Arava®)

- Newer DMARD
- Inactive and converted to A177-1726 in the GI tract and liver
Leflunomide (Arava®)

• A77-1726 inhibits the activity of dihydro-orotate dehydrogenase, an important enzyme in the de novo synthesis of pyrimidines.
Leflunomide (Arava®)

• Dose and Administration
  – 10 & 20 mg Tablets
  – Given daily – ranges from 10-20 mg per day

• Onset of Action
  – 6-8 weeks

• Avoid
  – Pregnancy – Teratogenic
    • *cholestyramine*
  – Alcohol
Leflunomide (Arava®)

• Common S/E
  – Diarrhea, nausea, malaise, hypertension, alopecia, rash

• Rare S/E
  – Liver: Follow enzymes – not usually a problem
  – Bone Marrow: Follow bloodwork – dose/sensitivity related
  – Infection
  – Pregnancy
  – Malignancy
Leflunomide (Arava®)

• Leflunomide 20 mg tablet PO OD – If side effects can:
  – Reduce to 10 mg PO OD or
  – Reduce to 20 mg every other day (Cheaper)

• Lab Monitoring (monthly initially)
  – CBC, ESR, CRP
  – AST, ALT, ALP, Albumin
  – Cr
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<td>Azathioprine</td>
<td>bone marrow suppression, hepatotoxicity, GI symptoms</td>
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- AZA is used when disease activity persists on other DMARDs
- May be safer than MTX for patients > 65 years with renal insufficiency
- PO dose: 50-100 mg qd (max 2.5 mg/kg/day)
- **Major Drug Interaction: Allopurinol**
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<td>Cyclophosphamide</td>
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<td>hemorrhagic cystitis, malignancy, infertility</td>
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- Oral immunosuppressive agent with significant toxicity profile
- Used in severe vasculitis and other extra-articular involvement
- PO dose: 50-100 mg qd (max 2.5 mg/kg/day)
Sulfasalazine

Salicylate (5-ASA)

Sulfinpyradone
Sulfasalazine (Not common)

- Developed in the late 1930s by Dr. Nana Svartz (Swedish Rheumatologist) for the treatment of “infective polyarthritis”
- Anti-inflammatory: Salicylic Acid
- Antibiotic: Sulfapyridine
- Sulfasalazine consists of salicylic acid and sulfapyridine joined by an azo bond.
- Sulfinpyradone is thought to be the active ingredient although, in RA, the mechanism of action is not understood
Sulfasalazine

• Pills taken twice daily (CPS and some pharmacists – QID!)
• Start at a low dose 1 per day and gradually work up to 4 per day
• Takes 6-8 weeks to work
• Common S/E: Malaise, Nausea, Abd pain, Rash, headaches, dizziness
• Rare S/E:
  – Hypersensitivity reaction
  – Liver: Follow enzymes – not usually a problem
  – Bone Marrow: Follow bloodwork – dose/sensitivity related
  – Renal: Very Rare
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Biologics Agents

• Specially designed to treat inflammatory types of arthritis such as rheumatoid and psoriatic arthritis.

• Work by different mechanisms.

• Like DMARDs, biologics are used to suppress inflammation and help prevent damage to the joint.
Biologic DMARD’s – Genetically Engineered Targeted Molecules Similar or Identical to Naturally Occurring Molecules

- **TNFα antagonists:**
  - Adalimumab (Humira)
  - Etanercept (Enbrel)
  - Infliximab (Remicade)
  - Certolizumab (Cimzia)
  - Golimumab (Simponi)

- **Interleukin-1 antagonist**
  - Anakinra (Kineret)

- **Suppress T-Cell activation**
  - Abatacept (Orencia)

- **Anti B-Cell monoclonal antibody**
  - Rituximab (Rituxan)
Role of Tumor Necrosis Factor in Rheumatoid Arthritis

- Bone resorption
- Joint inflammation
- Cartilage degradation
- Bone erosion
- Pain/joint inflammation
- Joint space narrowing
TNF inhibitors

- Infliximab
  - Murine Fv
  - Human Fcγ1

- Etanercept
  - Human TNFR2
  - Human Fcγ1

- Adalimumab
  - Human Fv
  - Human Fcγ1

- Certolizumab pegol
  - Humanized Fv (murine CDRs)
  - Polyethylene glycol

- Golimumab
  - Human Fv
  - Fab'
### TNF Inhibitors Approved for RA in the United States

<table>
<thead>
<tr>
<th>TNF Inhibitor</th>
<th>Structure</th>
<th>Typical Dosage, Route of Administration</th>
</tr>
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<tbody>
<tr>
<td>Infliximab&lt;sup&gt;4&lt;/sup&gt;</td>
<td>Chimeric MAb</td>
<td>3–10 mg/kg every 4–8 weeks, IV</td>
</tr>
<tr>
<td>Etanercept&lt;sup&gt;5&lt;/sup&gt;</td>
<td>Dimeric fusion protein p75 TNF receptor</td>
<td>50 mg weekly, SC</td>
</tr>
<tr>
<td>Adalimumab&lt;sup&gt;6&lt;/sup&gt;</td>
<td>Recombinant human MAb</td>
<td>40 mg biweekly, SC</td>
</tr>
<tr>
<td>Certolizumab pegol&lt;sup&gt;7&lt;/sup&gt;</td>
<td>Recombinant humanized antibody Fab’ fragment</td>
<td>200 mg biweekly or 400 mg monthly, SC</td>
</tr>
<tr>
<td>Golimumab&lt;sup&gt;8&lt;/sup&gt;</td>
<td>Recombinant human MAb</td>
<td>50 mg monthly, SC</td>
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</table>
Infliximab: Mechanism of Action

- Binds and neutralizes both soluble and membrane bound TNFα - inhibits further activity

![Diagram of TNFα binding and neutralization](Image)
T-Cell Co-Stimulatory Blockade (Abatacept)
Antigen presenting cell (APC)

- CD80/86
- Co-stimulatory pathway
- CD28

Major histocompatibility complex (MHC)

T cell receptor (TCR)

Fully activated T cell
ORENCIA modulates a key co-stimulatory signal required for full T-cell activation.
B-Cell Depletion (Rituximab)
B-Cell Depletion Therapy in RA

• How does B-Cell Depletion work?
  – B-Cells cannot act as antigen presenting cells to activate T-Cells
  – B-Cells cannot produce Rheumatoid Factor
  – B-Cells cannot release cytokines
Practical Aspects

• Given as two (2) infusions of 1000mg spaced two weeks apart
• All patients given 100 mg of solumedrol with each infusion
• Takes about 3-4 months to kick in
• Time to re-treatment – 6 to 9 months
IL-6 Has Numerous Articular Effects in RA

- **Antibody production**
- **B-cell**
- **Synoviocytes**
- **VEGF**
- **Endothelial cells**
- **Pannus formation**
- **Joint destruction**
- **Osteoclast activation**
- **Bone resorption**

**Mediation of chronic inflammation**

Tocilizumab

- Humanized mAb IgG1 (MW ~150 kd)
- Key Features:
  - Binds soluble and membrane bound IL-6R
  - Weak/no CDC* or ADCC** effector functions (*in vitro*)

*CDC: complement-dependent cytotoxicity
**ADCC: antibody-dependent cellular cytotoxicity
Safety Considerations with Biologic DMARD’s

- Serious Infections
- Opportunistic infections (TB)
- Malignancies/lymphoma
- Demyelination
- Hematologic abnormalities

- Administration reactions
- Congestive heart failure
- Hepatic
- Autoantibodies and drug-induced lupus
- Vaccination
Biologics: Relative Contraindications

- Active Hepatitis B Infection
- Multiple sclerosis, optic neuritis
- Active serious infections
- Chronic or recurrent infections
- Current neoplasia
- History of TB or positive PPD (untreated)
- Congestive heart failure (Class III or IV)
Cumulative incidence of tuberculosis (TB) following first exposure to anti-tumour necrosis factor (anti-TNF) therapy (most recent drug model, with person-years censored at death, last returned follow-up form, or date of switching to second anti-TNF).


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## Dosages, costs, and approximate time to benefit of disease-modifying antirheumatic drugs used in the treatment of rheumatoid arthritis

<table>
<thead>
<tr>
<th>Drug</th>
<th>Approximate time to benefit</th>
<th>Usual maintenance dose</th>
<th>Annual drug cost (cost of generics), dollars*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydroxychloroquine</td>
<td>2-6 months</td>
<td>200 mg twice a day</td>
<td>1,056 (559)</td>
</tr>
<tr>
<td>Sulfasalazine</td>
<td>1-3 months</td>
<td>1,000 mg 2-3 times a day</td>
<td>509-763 (205-308)</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>1-2 months</td>
<td>Oral 7.5-20 mg/week; injectable 7.5-20 mg/week</td>
<td>697-1,859 (259-691);419-806 (42-81)</td>
</tr>
<tr>
<td>Leflunomide</td>
<td>4-12 weeks (skewed earlier)</td>
<td>20 mg/day in a single dose, if tolerated; otherwise, 10 mg/day†</td>
<td>2,938</td>
</tr>
<tr>
<td>Etanercept</td>
<td>A few days to 12 weeks</td>
<td>25 mg subcutaneously twice a week</td>
<td>15,436</td>
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<tr>
<td>Infliximab plus oral and</td>
<td>A few days to 4 months</td>
<td>3-10 mg IV every 8 weeks or 3-5 mg IV every 4 weeks‡</td>
<td>13,940-30,287 or 28,040-36,694§</td>
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<tr>
<td>subcutaneous methotrexate</td>
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<tr>
<td>Azathioprine</td>
<td>2-3 months</td>
<td>50-150 mg/day</td>
<td>579-1,737 (471-1,414)</td>
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<tr>
<td>D-penicillamine</td>
<td>3-6 months</td>
<td>250-750 mg/day</td>
<td>865-2,595 (398-1,194)</td>
</tr>
<tr>
<td>Gold, oral</td>
<td>4-6 months</td>
<td>3 mg twice a day</td>
<td>1,622</td>
</tr>
<tr>
<td>Gold, intramuscular</td>
<td>3-6 months</td>
<td>25-50 mg intramuscularally every 2-4 weeks¶</td>
<td>198# (142)</td>
</tr>
<tr>
<td>Minocycline</td>
<td>1-3 months</td>
<td>100 mg twice a day</td>
<td>2,592 (582)</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>2-4 months</td>
<td>2.5-4 mg/kg/day**</td>
<td>4,432-8,859 (3,512-7,022)</td>
</tr>
<tr>
<td>Staphylococcal protein A</td>
<td>3 months</td>
<td>Weekly for 12 weeks</td>
<td>20,433††</td>
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<td>immunoadsorption</td>
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Treatment Summary

- Early appropriately aggressive intervention in patients with inflammatory arthritis: critical to best possible outcome.

- The combination of a biologic plus MTX is frequently more effective than either agent alone.
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# DISEASE MODIFYING ANTIRHEUMATIC DRUGS

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<td><strong>B cell depleting agent</strong></td>
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55 YOF complains of months of bilateral hand pain. She describes progressive morning stiffness lasting 3 hours with wrist and MCP pain and swelling. She has also noted some discomfort and perhaps swelling in her wrists, shoulders, knees, and toes. Review of systems is unremarkable.

- PMHx: GERD, PUD
- Family History: adopted, No Etoh or other drugs
- Labs: CBC normal, elevated Scr (1.7 mg/dl) RF positive

A/P: Pt was given high dose NSAIDs with some improvement and referred to Rheumatology.
Early Arthritis- case scenario

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- Social Hx: + tobacco
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- Hand XRAY-s: no abnormalities

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