Chronic Inflammatory Disease: An Introduction

Developed by
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Presented by
Mike Crowe, PharmD, MBA, CSP, FMPA

Speaker Disclosure

Michael Crowe has nothing to disclose.
Objectives

1. Summarize available treatments for the chronic inflammatory diseases (CIDs) rheumatoid arthritis (RA), plaque psoriasis, and Crohn’s disease.

2. Describe the etiology of CIDs.

3. Outline the pathophysiology of CIDs.

4. Explain the pharmacologic approach to treating CIDs.

Chronic Inflammatory Diseases (CIDs)
Immunology Introduction

Rheumatoid Arthritis
Psoriasis
Inflammatory Bowel Disease

Tumor Necrosis Factor (TNF)-α Inhibitors

<table>
<thead>
<tr>
<th>Medication Name Drug Class</th>
<th>Route</th>
<th>Rheumatoid Arthritis</th>
<th>Plaque Psoriasis</th>
<th>Psoriatic Arthritis</th>
<th>Crohn's Disease</th>
<th>Ulcerative Colitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Remicade® (infliximab) TNFα Inhibitor</td>
<td>IV</td>
<td>✓ *&lt;br&gt;q 4-8 wks</td>
<td>✓ *&lt;br&gt;q 8 wks</td>
<td>✓ *&lt;br&gt;q 8 wks</td>
<td>✓ *&lt;br&gt;q 8 wks</td>
<td>✓ *&lt;br&gt;q 8 wks</td>
</tr>
<tr>
<td>Enbrel® (etanercept) TNFα Inhibitor</td>
<td>SC</td>
<td>✓&lt;br&gt;q week</td>
<td>✓ *&lt;br&gt;q week</td>
<td>✓&lt;br&gt;q week</td>
<td>✓&lt;br&gt;q week</td>
<td>✓&lt;br&gt;q week</td>
</tr>
<tr>
<td>Humira® (adalimumab) TNFα Inhibitor</td>
<td>SC</td>
<td>✓&lt;br&gt;q 1 or 2 wks</td>
<td>✓ *&lt;br&gt;qow</td>
<td>✓&lt;br&gt;qow</td>
<td>✓ *&lt;br&gt;qow</td>
<td>✓ *&lt;br&gt;qow</td>
</tr>
<tr>
<td>Simponi® [Aria™] (golimumab) TNFα Inhibitor</td>
<td>SC [IV]</td>
<td>✓ [*]&lt;br&gt;MTX q 4 [8] wks</td>
<td>✓&lt;br&gt;q 4 wks</td>
<td>✓&lt;br&gt;q 4 wks</td>
<td>✓ *&lt;br&gt;q 4 wks</td>
<td>✓ *&lt;br&gt;q 4 wks</td>
</tr>
<tr>
<td>Cimzia® (certolizumab pegol) TNFα Inhibitor</td>
<td>SC</td>
<td>✓ *&lt;br&gt;q 2 or 4 wks</td>
<td>✓ *&lt;br&gt;qow</td>
<td>✓ *&lt;br&gt;q 4 wks</td>
<td>✓ *&lt;br&gt;q 4 wks</td>
<td></td>
</tr>
</tbody>
</table>

*Induction dose is indicated; MTX = dosed with methotrexate


<table>
<thead>
<tr>
<th>Specialty Medications for CIDs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Medication Name</strong></td>
</tr>
<tr>
<td>Kineret® (anakinra) IL-1 Inhibitor</td>
</tr>
<tr>
<td>Actemra® (tocilizumab) IL-6 Inhibitor</td>
</tr>
<tr>
<td>Cosentyx® (secukinumab) IL-17A inhibitor</td>
</tr>
<tr>
<td>Taltz™ (ixekizumab) IL-17A Inhibitor</td>
</tr>
<tr>
<td>Stelara® (ustekinumab) IL-12/23 Inhibitor</td>
</tr>
<tr>
<td>Otezla® (apremilast) PDE-4 Inhibitor</td>
</tr>
</tbody>
</table>

*Induction dose is indicated; MTX = dosed with methotrexate


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<table>
<thead>
<tr>
<th>Specialty Medications for CIDs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Medication Name</strong></td>
</tr>
<tr>
<td>Xeljanz® [XR] (tofacitinib) JAK Inhibitor</td>
</tr>
<tr>
<td>Rituxan® (rituximab) CD20 of B cell</td>
</tr>
<tr>
<td>Orencia® (abatacept) CD80/CD86 of T cell</td>
</tr>
<tr>
<td>Tysabri® (natalizumab) Integrin Antagonist</td>
</tr>
<tr>
<td>Entyvio® (vedolizumab) Integrin Receptor Antagonist</td>
</tr>
</tbody>
</table>

*Induction dose is indicated; MTX = dosed with methotrexate


Biologic Product Safety

### Common Adverse Effects
- Infection
  - Upper respiratory tract
  - Sinusitis
- Injection site reactions
  - Pain, redness, itching
  - Infusion reactions
- Headache

### Warnings/Precautions
- Serious infections
- Hepatitis B virus reactivation
- Allergic reactions
- Malignancies
- Moderate to severe CHF
  - TNFα Inhibitors
- Demyelinating disease
- Few drug interactions

Self-Administered Biologic Products

### Injection technique
- Remove device from fridge for 15-30 minutes prior to injection
- Wash and dry hands
- Select an appropriate injection site
- Do not inject into skin that is bruised, sore, red, or hard
- If you have psoriasis, do not inject directly into any lesions
- Rotate injection sites each time you inject
- Wipe the injection site with an alcohol swab and allow area to dry
- Inject using the technique appropriate for the specific device
- Dispose the device in a sharps disposal container immediately after use
- Do not rub the injection site
Biologic Product Counseling Points

- Storage
- Avoid live vaccines during treatment
- Notify physician of signs/symptoms of the following:
  - Infection
  - Hypersensitivity
  - Hepatitis B reactivation
  - Heart failure
  - Demyelination
  - Malignancy
- Expectations


Chronic Inflammatory Disease

RHEUMATOID ARTHRITIS
Rheumatoid Arthritis

- Chronic autoimmune disorder of the joints
- Symmetrical presentation
  - Painful inflammation
  - Joint deformity
- 1.3 million affected in US
  - Women > Men (3:1)
- Races equally affected


Articular Presentation

- Pain/tenderness
- Swelling
- Morning stiffness
- Walking difficulties
- Joint deformity

Hands   Wrist
Elbows  Shoulders
Knees   Ankles

Pathophysiology

- Immune System Fails to Recognize Self
- Increased Inflammatory Response
- Inflammation of Synovial Tissues
- Cartilage and Bone Erosion

Rheumatoid Arthritis Treatment Options

**Symptomatic Therapies**

- Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)
- Corticosteroids

**Disease Modifying Antirheumatic Drugs (DMARDs)**

- Traditional DMARDs
- Biologics

American College of Rheumatology Guidelines

DMARD monotherapy

DMARD = disease-modifying antirheumatic drug (includes hydroxychloroquine [HCQ], leflunomide [LEF], methotrexate [MTX], and sulfasalazine [SSZ])

Anti-TNF = anti–tumor necrosis factor (TNFα inhibitor)

* Treatment target should ideally be low disease activity or remission

‡ Consider adding short-term glucocorticoids (defined as <3 months) for RA disease flares.

Combination DMARD therapy with 2 DMARDs, which is most commonly MTX based, with some exceptions (e.g., MTX + HCQ, MTX + LEF, MTX + sulfasalazine, and sulfasalazine + HCQ), and triple therapy (MTX + HCQ + sulfasalazine)


Traditional DMARD Counseling

<table>
<thead>
<tr>
<th>Counseling</th>
<th>MTX</th>
<th>LEF</th>
<th>SSZ</th>
<th>HCQ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avoid pregnancy (women/partners)</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Take with food</td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Hydrate and report renal toxicity</td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Urine/skin discoloration may occur</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Report vision changes</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>May cause photosensitivity</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Report rashes immediately</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatic toxicity</td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>GI toxicity</td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Hematologic toxicity</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

## TNFα Inhibitors

<table>
<thead>
<tr>
<th>Agent</th>
<th>Route</th>
<th>Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Remicade® (infliximab)</td>
<td>IV</td>
<td>3-10 mg/kg at weeks 0, 2, and 6 then every 8 weeks</td>
</tr>
<tr>
<td>Humira® (adalimumab)</td>
<td>SC</td>
<td>40 mg every week or every other week</td>
</tr>
<tr>
<td>Enbrel® (etanercept)</td>
<td>SC</td>
<td>50 mg weekly or 25 mg sc twice weekly</td>
</tr>
<tr>
<td>Simponi® (golimumab)</td>
<td>SC</td>
<td>50 mg monthly</td>
</tr>
<tr>
<td>Cimzia® (certolizumab pegol)</td>
<td>SC</td>
<td>400 mg at weeks 0, 2, and 4 then 200 mg every other week</td>
</tr>
</tbody>
</table>

## Non-TNFα Products

<table>
<thead>
<tr>
<th>Agent</th>
<th>Route</th>
<th>Dosing</th>
</tr>
</thead>
</table>
| Orencia® (abatacept)   | IV/SC       | IV: Adults weighing >100 kg: 1000 mg IV weeks 0, 2, and 4 then every 4 weeks after  
|                        |             | SC: 125 mg once weekly with or without IV loading dose                |
| Kineret® (anakinra)    | SC          | 100 mg once daily                                                       |
| Rituxan® (rituximab)   | IV          | 1000 mg on days 1 and 15; administer subsequent courses every 16-24 weeks |
| Actemra® (tocilizumab) | IV/SC       | IV: 4 mg/kg every 4 weeks                                               |
|                        |             | SC: Adults weighing <100 kg: 162 mg every other week; may increase to weekly |
|                        |             | SC: Adults weighing >100 kg: 162 mg weekly                               |
| Xeljanz® (tofacitinib) | PO          | IR tablet: 5 mg twice daily                                             |
|                        |             | ER tablet: 11 mg once daily                                             |
RA Treatment Goals and Efficacy Evaluation

**Health Assessment Questionnaire II (HAQ-II)**
- 10-item validated questionnaire
- Common tool for measuring functioning status in rheumatology
- Looks at difficulty of completing common activities of daily living

**Routine Assessment of Patient Index Data (RAPID) 3**
- Validated patient questionnaire
- Uses the multidimensional HAQ (MD-HAQ)

**Patient Activity Scale (PAS)**
- Validated patient questionnaire
- Includes the HAQ-II

**Chronic Inflammatory Disease**

**PSORIASIS**
Psoriasis (PsO)

- Chronic, inflammatory, autoimmune disease of skin
- Hallmark sign is plaques
  - Irritating, painful, emotionally debilitating
- Concurrent joint involvement
  - Psoriatic arthritis (PsA)
- 7.4 million affected in US (~2% of population)
- Genders equally affected
- Prevalence difference by race
- Onset typically 15-35 years of age


Pathphysiology

- Inappropriate autoreactive T-cell activation
- Release of growth factors and inflammatory cytokines
- Increased rate of skin cell proliferation

The skin cell cycle is shortened almost 10-fold, from an average of 311 hours to just 36 hours.


### Disease Severity

**Mild**
Mild psoriasis covers less than 3 percent of the body

**Moderate**
Moderate psoriasis covers between 3 and 10 percent of the body

**Severe**
Severe psoriasis covers more than 10 percent of the body

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### Psoriasis Treatment Options

**Topical**
- Creams & Ointments
- Light Therapy

**Systemic**
- Traditional Oral
- Biologics

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*Thomas CL, Finlay AY. The “handprint” approximates to 1% of the total body surface area whereas the “palm minus the fingers” does not. *Br J Dermatol.* 2007;157(5):1080-1081.*


### Treatment Guidelines

- **Limited PsO**
  - Topicals or Targeted Phototherapy
  - UVB/PUVA

- **Extensive PsO**
  - Systemic
  - Biologic

- **PsO with PsA**
  - TNF+/- MTX
  - UVB/PUVA

Lack of Effect

TNF= tumor necrosis factor inhibitor; MTX = methotrexate; PsA = psoriatic arthritis

### Topical and Oral Systemic Psoriasis Treatments

<table>
<thead>
<tr>
<th>Category</th>
<th>Potential Therapies</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Topical Therapies</strong></td>
<td>Retinoids (Tazarac®)  Corticosteroids  Vitamin D Analogs  Calcipotriene  Calcitriol</td>
</tr>
<tr>
<td>AAD-Preferred</td>
<td>Calcineurin Inhibitors  Keratolytics  Coal tar  Anthralin</td>
</tr>
<tr>
<td>Alternatives</td>
<td></td>
</tr>
<tr>
<td><strong>Traditional Oral Systemic Therapies</strong></td>
<td>Methotrexate  Cyclosporine  Acitretin (Soriatane®)</td>
</tr>
<tr>
<td></td>
<td>Leflunomide  Sulfasalazine  Tacrolimus  Azathioprine  Hydroxyurea  Mycophenolate</td>
</tr>
</tbody>
</table>


### TNFα Inhibitor Therapies

<table>
<thead>
<tr>
<th>Agent</th>
<th>Route</th>
<th>Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Humira® (adalimumab)</strong></td>
<td>SC</td>
<td>• 80 mg at week 0&lt;br&gt;• 40 mg on week 1 and every other week</td>
</tr>
<tr>
<td><strong>Enbrel® (etanercept)</strong></td>
<td>SC</td>
<td>• 50 mg twice weekly for 3 months then by 50 mg once weekly</td>
</tr>
<tr>
<td><strong>Remicade® (infliximab)</strong></td>
<td>IV</td>
<td>• 5 mg/kg at 0, 2 and 6 weeks, then every 8 weeks</td>
</tr>
</tbody>
</table>


### IL-Targeting Therapies

<table>
<thead>
<tr>
<th>Agent/Target</th>
<th>Route</th>
<th>Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Taltz™ (ixekizumab)</strong> IL-17A</td>
<td>SC</td>
<td>• 160 mg at week 0&lt;br&gt;• 80 mg at weeks 2, 4, 6, 8, 10, and 12 then 80 mg every 4 weeks</td>
</tr>
<tr>
<td><strong>Cosentyx® (secukinumab)</strong> IL-17A</td>
<td>SC</td>
<td>• 300 mg weeks 0, 1, 2, 3, and 4 then 300 mg every 4 weeks A dose of 150 mg may be acceptable for some patients</td>
</tr>
<tr>
<td><strong>Stelara® (ustekinumab)</strong> IL-12/23</td>
<td>SC</td>
<td>For patients weighing ≤100 kg (220 lbs)&lt;br&gt;•45 mg initially and 4 weeks later&lt;br&gt;•45 mg every 12 weeks&lt;br&gt;Use 90 mg for patients weighing &gt;100 kg</td>
</tr>
</tbody>
</table>

PDE4-Targeting Therapies

<table>
<thead>
<tr>
<th>Agent/Target</th>
<th>Route</th>
<th>Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Otezla® (apremilast) PDE4</td>
<td>PO</td>
<td>30 mg twice daily after completion of 5-day titration dosing:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Day 1: 10 mg in AM</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Day 2: 10 mg in AM, 10 mg in PM</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Day 3: 10 mg in AM, 20 mg in PM</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Day 4: 20 mg in AM, 20 mg in PM</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Day 5: 20 mg in AM, 30 mg in PM</td>
</tr>
</tbody>
</table>


Treatment Goals

**Primary Goal**
- Skin normalization

**Secondary Goals**
- Itching relief
- Reducing flare-ups
- Managing adverse events
- Improving quality of life

**Treat-to-Target**
- Body surface area (BSA)
- Evaluate 3 months post-new therapy
- Acceptable response: BSA 3% or less or 75% improvement in BSA

- Target response: BSA 1% or less
- Evaluate every 6 months during maintenance period


Chronic Inflammatory Disease

INFLAMMATORY BOWEL DISEASES

Etiology

• Irritable bowel disease (IBD) most prevalent in Western Countries
  • Crohn’s Disease (CD) Incidence
    • 6 - 15.5 cases per 100,000 persons/year
  • Ulcerative colitis (UC) Incidence
    • 1.2 - 20 cases per 100,000 persons/year

• Males and females equally affected by IBD
  • 20-30% more women CD
  • 60% more men UC
Presentation

- Malaise and fever
- Mild abdominal cramping
- Frequent small-volume bowel movements
- Weight loss and malnutrition
- Hematochezia common with colonic involvement

Distinguishing Factors

<table>
<thead>
<tr>
<th>Ulcerative Colitis (UC)</th>
<th>Crohn’s Disease (CD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Confined to rectum and colon</td>
<td>• Any part of GI tract</td>
</tr>
<tr>
<td>• Continuous lesions</td>
<td>• Discontinuous lesions</td>
</tr>
<tr>
<td>• Mucosa and submucosa affected</td>
<td>• Transmural process</td>
</tr>
<tr>
<td></td>
<td>– Fistulas</td>
</tr>
<tr>
<td></td>
<td>– Perforations</td>
</tr>
<tr>
<td></td>
<td>– Strictures</td>
</tr>
</tbody>
</table>


IBD Treatment Options

**Topical**
- Enemas
- Suppositories

**Systemic**
- Traditional Oral
- Biologics
- Traditional IV

**Surgical Intervention**

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**Traditional Treatment Options**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Brand Name(s)</th>
<th>Indication(s)</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azathioprine</td>
<td>Imuran®</td>
<td>CD, UC</td>
<td>1.5–2.5 mg/kg per day orally</td>
</tr>
<tr>
<td>Budesonide</td>
<td>Various</td>
<td>CD, UC</td>
<td>Varies by formulation</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>Sandimmune®</td>
<td>CD, UC</td>
<td>4 mg/kg per day IV continuous infusion</td>
</tr>
<tr>
<td>Mercaptopurine</td>
<td>Purinethol®</td>
<td>CD, UC</td>
<td>1.5–2.5 mg/kg per day orally</td>
</tr>
<tr>
<td>Mesalamine</td>
<td>Various</td>
<td>CD, UC</td>
<td>Varies by formulation</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>Trexall®</td>
<td>CD</td>
<td>15–25 mg weekly (IM/SC/orally)</td>
</tr>
<tr>
<td>Sulfasalazine</td>
<td>Sulfazine®</td>
<td>UC</td>
<td>3-4 grams/day divided TID</td>
</tr>
</tbody>
</table>

Appropriate treatment options and dosing vary based on disease location, severity, presence of complications, induction vs. maintenance and other patient-specific factors.

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# TNFα Inhibitor Therapies

<table>
<thead>
<tr>
<th>Medication Drug Class</th>
<th>Route</th>
<th>Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Remicade® (infliximab) TNFα Inhibitor</td>
<td>IV</td>
<td>UC/CD: 5 mg/kg week 0, 2, and 6 then every 8 weeks</td>
</tr>
<tr>
<td>Humira® (adalimumab) TNFα Inhibitor</td>
<td>SC</td>
<td>UC/CD: 160 mg on day 1, 80 mg at week 2, then 40 mg every other week</td>
</tr>
<tr>
<td>Simponi® (golimumab) TNFα Inhibitor</td>
<td>SC</td>
<td>UC: 200 mg day 1, then 100 mg two weeks later then every 4 weeks starting at week 6</td>
</tr>
<tr>
<td>Cimzia® (certolizumab pegol) TNFα Inhibitor</td>
<td>SC</td>
<td>CD: 400 mg at week 0, 2, 4, then every 4 weeks</td>
</tr>
</tbody>
</table>


# Non-TNF Inhibitor Biologics

<table>
<thead>
<tr>
<th>Medication Drug Class</th>
<th>Dosing</th>
<th>Counseling Points</th>
</tr>
</thead>
</table>
| Tysabri® (natalizumab) | CD: 300 mg IV every 4 weeks | • Available only through the TOUCH™ Prescribing Program (REMS program)  
• Has been linked to cases of PML  
• Report signs/symptoms of infection  
• Report signs/symptoms of hepatotoxicity |
| Stelara® (ustekinumab) | CD: Induction: ≤55 kg: 260 mg IV, 56-85 kg: 390 mg IV, >85 kg: 520 mg IV  
Maintenance: 90 mg SC every 8 weeks thereafter | (Please refer to psoriasis section) |
| Entyvio® (vedolizumab) | CD/UC: 300 mg IV at weeks 0, 2, 6 then every 8 weeks thereafter | • Hypersensitivity reactions  
• Has been linked to cases of PML  
• Report signs/symptoms of infection |


IBD Treatment Goals and Efficacy Evaluation

• Goals of treatment
  • Resolve inflammation and complications
  • Alleviate systemic manifestations
  • Maintain remission
• Measures of treatment effectiveness
  • Crohn’s Disease Activity Index (CDAI)
  • Harvey Bradshaw Index (HBI)
  • Inflammatory Bowel Disease Questionnaire (IBDQ)

Conclusion

• CIDs result from overactive or malfunctioning immune system
• Mild disease can usually be treated with non-targeted, non-specialty meds
• Moderate to severe disease often includes oral and/or biologic targeted therapies
  – Symptom management
  – Non-curative