Curricular Track I—Immunomodulation in Rheumatology and Gastrointestinal Diseases
Activity No. 0217-0000-11-105-L01-P (Knowledge-Based Activity)

Wednesday, October 19
10:15 a.m.–11:45 a.m.
Convention Center: Rooms 304 & 305

Moderator: Eric M. Tichy, Pharm.D., BCPS
Clinical Pharmacy Specialist, Solid Organ Transplant, Yale-New Haven Hospital, New Haven, Connecticut

Agenda

10:15 a.m. Immunotherapy in Rheumatology: Targeting Inflammation and Disease Progression
Lauren K. McCluggage, Pharm.D., BCPS
Assistant Professor, Department of Pharmacy Practice, Lipscomb University College of Pharmacy, Nashville, Tennessee

11:00 a.m. Current and Emerging Immunotherapy for Gastrointestinal Diseases
Geoffrey C. Wall, Pharm.D., FCCP, BCPS
Internal Medicine Clinical Pharmacist, Iowa Methodist Medical Center; Associate Professor of Pharmacy Practice, Drake University College of Pharmacy, Des Moines, Iowa

Faculty Conflict of Interest Disclosures
Lauren K. McCluggage: no conflicts to disclose.
Geoffrey C. Wall: no conflicts to disclose.

Learning Objectives

1. Review current trends in management of rheumatoid arthritis.
2. Discuss the role of tumor necrosis factor alpha in rheumatologic disease.
3. Differentiate disease-modifying antirheumatic drug regimens based on the biologic and non-biologic properties.
4. Discuss the unique considerations related to immunotherapy toxicity associated with treatment of rheumatoid arthritis.
5. Discuss the role of immunomodulation for Crohn’s Disease and Ulcerative Colitis.
6. Identify short and long-term complications of immunomodulatory therapy used for gastrointestinal disorders.

Self-Assessment Questions

Self-assessment questions are available online at www.accp.com/am
Immunotherapy in Rheumatology: Targeting Inflammation and Disease Progression

Lauren McCluggage, Pharm.D., BCPS
Assistant Professor
Department of Pharmacy Practice
Lipscomb University College of Pharmacy
Conflicts of Interest

NOTHING TO DISCLOSE.
Objectives

- Review current trends in management of rheumatoid arthritis (RA)
- Discuss the role of tumor necrosis factor (TNF) alpha in RA
- Differentiate disease-modifying antirheumatic drug (DMARD) regimens based on the biologic and non-biologic properties
- Discuss the unique considerations related to immunotherapy toxicity associated with treatment of RA
# RA Treatments

<table>
<thead>
<tr>
<th>Anti-inflammatory Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSAIDs</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Traditional DMARDs</th>
</tr>
</thead>
<tbody>
<tr>
<td>DMARDs</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Other antirheumatic drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gold derivatives, cyclosporine, minocycline</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Biological DMARDs</th>
</tr>
</thead>
<tbody>
<tr>
<td>TNF alpha inhibitors</td>
</tr>
<tr>
<td>IL-1 inhibitors</td>
</tr>
<tr>
<td>Costimulation blocker</td>
</tr>
<tr>
<td>B-cell targeted therapy</td>
</tr>
<tr>
<td>IL-6 receptor antagonist</td>
</tr>
</tbody>
</table>
Pathophysiology

Disease Evaluation

- **Disease Activity Score (DAS) 28**
  - 0-9.4 (≤3.2: low disease activity)
  - Tender joints, swollen joints, ESR or CRP, visual analog score

- **American College of Rheumatology (ACR) 70**
  - 70% improvement in tender and swollen joints
  - 70% improvement in 3 of 5
    - Patient pain, patient global assessment, physician global assessment, patient self-assessed disability, acute phase reactants
ACR: Duration <6 months

Disease Activity

Low

Moderate

High

Poor Prognostic Features

Cost Limitations

<3 mo

3-6 mo

Anti-TNF + MTX

### ACR: Duration >6 months

<table>
<thead>
<tr>
<th>Disease Activity</th>
<th>Low</th>
<th>Moderate</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poor Prognostic Factors</td>
<td>-/-+</td>
<td>-/-+</td>
<td>-/-+</td>
</tr>
<tr>
<td>Duration: 6-24 months</td>
<td>HCQ, LEF, MTX, SSZ, MTX+SSZ+HCQ</td>
<td>LEF, MTX, SSZ, MTX+HCQ, MTX+SSZ, MTX+LEF, MTX+SSZ+HCQ</td>
<td>SSZ, SSZ+HCQ, Lef, MTX, MTX+HCQ, MTX+SSZ, MTX+LEF, MTX+SSZ+HCQ</td>
</tr>
<tr>
<td>Duration: &gt;24 months</td>
<td>LEF, MTX, SSZ, MTX+HCQ, MTX+LEF, SSZ+HCQ</td>
<td>LEF, MTX, SSZ, MTX+HCQ</td>
<td>SSZ, Lef, MTX, MTX+HCQ, MTX+SSZ, MTX+LEF, MTX+SSZ+HCQ</td>
</tr>
<tr>
<td>Failed MTX monotherapy</td>
<td>Non-biologic OR Anti-TNF</td>
<td>Anti-TNF</td>
<td>Non-biologic OR Anti-TNF</td>
</tr>
<tr>
<td>Failed MTX combo therapy or sequential DMARDs</td>
<td>Non-biologic OR Anti-TNF</td>
<td>Abatacept Anti-TNF</td>
<td>Non-biologic OR Anti-TNF</td>
</tr>
</tbody>
</table>

## Treat Aggressively

<table>
<thead>
<tr>
<th>FIN-RACo</th>
<th>SSZ + HCQ + MTX + prednisolone</th>
<th>SSZ + prednisolone</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACR remission – 2 yrs</td>
<td>37%</td>
<td>18%</td>
</tr>
<tr>
<td>ACR remission – 5 yrs</td>
<td>28%</td>
<td>22%</td>
</tr>
<tr>
<td>Remission ever – 11 yrs</td>
<td>68%</td>
<td>40%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>TICORA</th>
<th>Monthly monitoring and fixed adjustments</th>
<th>Monitoring every 3 months and prn adjustments</th>
</tr>
</thead>
<tbody>
<tr>
<td>EULAR remission – 1.5 yrs</td>
<td>65%</td>
<td>16%</td>
</tr>
</tbody>
</table>

Treat Early

## Treat Early

<table>
<thead>
<tr>
<th></th>
<th>Very Early Treatment</th>
<th>Late Early Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median disease duration</td>
<td>3 months</td>
<td>12 months</td>
</tr>
<tr>
<td>Change in DAS28</td>
<td>-2.72</td>
<td>-1.61</td>
</tr>
<tr>
<td>DAS28 ≤ 3.2</td>
<td>75%</td>
<td>35%</td>
</tr>
<tr>
<td>DAS28 &lt; 2.6</td>
<td>50%</td>
<td>15%</td>
</tr>
<tr>
<td>Change in Larsen scores</td>
<td>3.6</td>
<td>14.7</td>
</tr>
<tr>
<td>ACR70 response</td>
<td>55%</td>
<td>20%</td>
</tr>
</tbody>
</table>

**2010 ACR Classification**

- **> 1 joint with definite synovitis**
- **Synovitis not better explained by another disease**

<table>
<thead>
<tr>
<th>JOINT DISTRIBUTION (0-5)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1 large joint</td>
<td>0</td>
</tr>
<tr>
<td>2-10 large joints</td>
<td>1</td>
</tr>
<tr>
<td>1-3 small joints (large joints not counted)</td>
<td>2</td>
</tr>
<tr>
<td>4-10 small joints (large joints not counted)</td>
<td>3</td>
</tr>
<tr>
<td>&gt;10 joints (at least one small joint)</td>
<td>5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SEROLOGY (0-3)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative RF AND negative ACPA</td>
<td>0</td>
</tr>
<tr>
<td>Low positive RF OR low positive ACPA</td>
<td>2</td>
</tr>
<tr>
<td>High positive RF OR high positive ACPA</td>
<td>3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SYMPTOM DURATION (0-1)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;6 weeks</td>
<td>0</td>
</tr>
<tr>
<td>≥6 weeks</td>
<td>1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ACUTE PHASE REACTANTS (0-1)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal CRP AND normal ESR</td>
<td>0</td>
</tr>
<tr>
<td>Abnormal CRP OR abnormal ESR</td>
<td>1</td>
</tr>
</tbody>
</table>

>6 = definite RA

Treat to Target: T2T

- Treatment must be based on decision between patient and rheumatologist.
- Primary goal is to maximize quality of life by controlling symptoms, preventing structural damage and normalizing function and social participation.
- Suppressing inflammation is the most important way to achieve goals.
- Measuring disease activity and adjusting therapy optimizes outcomes.

Assess disease activity every 3-6 months

Remission

Assess disease activity every 1-3 months

Adapt Therapy

Low Disease Activity

Adapt therapy if state is lost

Sustained remission

Sustained low disease activity

Remission

- **T2T Definition**
  - Absence of signs and symptoms of significant inflammatory disease activity

- **2011ACR/EULAR Definition**

<table>
<thead>
<tr>
<th>Clinical Trials</th>
<th>Clinical Practice</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tender joint count (TJC) $\leq 1$</td>
<td>TJC $\leq 1$</td>
</tr>
<tr>
<td>Swollen joint count (SJC) $\leq 1$</td>
<td>SWJ $\leq 1$</td>
</tr>
<tr>
<td>PtGA* $\leq 1$</td>
<td>PtGA* $\leq 1$</td>
</tr>
<tr>
<td>C-reactive protein (CRP) $\leq 1$mg/dL</td>
<td></td>
</tr>
<tr>
<td>Simplified Disease Activity Index (SDAI) score $\leq 3.3$</td>
<td>Clinical Disease Activity Score (CDAI) $\leq 2.8$</td>
</tr>
</tbody>
</table>

*PtGA: patient global assessment 0-10 scale
SDAI = SJC + TJC + PtGA + Provider global assessment (PhGA) + CRP
CDAI = SJC + TJC + PtGA + PhGA

<table>
<thead>
<tr>
<th>Description</th>
<th>Adalimumab</th>
<th>Certolizumab</th>
<th>Etanercept</th>
<th>Golimumab</th>
<th>Infliximab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Description</td>
<td>Monoclonal antibody</td>
<td>Fab’ fragment</td>
<td>Dimeric TNF receptor + Fc</td>
<td>Monoclonal antibody</td>
<td>Monoclonal antibody</td>
</tr>
<tr>
<td>Fully humanized</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Route</td>
<td>SC</td>
<td>SC</td>
<td>SC</td>
<td>SC</td>
<td>IV</td>
</tr>
<tr>
<td>Frequency</td>
<td>q2 weeks</td>
<td>q2-4 weeks*</td>
<td>Weekly</td>
<td>Monthly</td>
<td>Every 8 weeks*</td>
</tr>
<tr>
<td>Indication</td>
<td>Moderate to severe</td>
<td>Moderate to severe</td>
<td>Moderate to severe with MTX</td>
<td>Moderate to severe with MTX</td>
<td>Moderate to severe with MTX</td>
</tr>
</tbody>
</table>

* Maintenance frequency after induction therapy
### Other Biologics

<table>
<thead>
<tr>
<th>Description</th>
<th>Abatacept</th>
<th>Anakinra</th>
<th>Rituximab</th>
<th>Tocilizumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Description</td>
<td>Costimulation modulator inhibits T-cell activation</td>
<td>IL-1 receptor antagonist</td>
<td>Monoclonal antibody against CD20 antigen</td>
<td>Monoclonal antibody against IL6</td>
</tr>
<tr>
<td>Fully humanized</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Route</td>
<td>IV or SC</td>
<td>SC</td>
<td>IV</td>
<td>IV</td>
</tr>
<tr>
<td>Frequency</td>
<td>q4 weeks or weekly</td>
<td>Daily</td>
<td>0 and 2 weeks then every 24 weeks</td>
<td>q4 weeks</td>
</tr>
<tr>
<td>Indication</td>
<td>Moderate to severe</td>
<td>Moderate to severe who have failed &gt;1 DMARD</td>
<td>Moderate to severe who have failed &gt;1 anti-TNF</td>
<td>Moderate to severe who have failed &gt;1 anti-TNF</td>
</tr>
</tbody>
</table>
Biologics in MTX Failure

ACR70 Response Rate

MTX + placebo  MTX + biologic

<table>
<thead>
<tr>
<th>Biologic</th>
<th>ACR70 Response Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adalimumab</td>
<td>3</td>
</tr>
<tr>
<td>Certolizumab</td>
<td>3</td>
</tr>
<tr>
<td>Etanercept</td>
<td>0</td>
</tr>
<tr>
<td>Golimumab</td>
<td>5</td>
</tr>
<tr>
<td>Infliximab</td>
<td>0</td>
</tr>
<tr>
<td>Tocilizumab</td>
<td>2</td>
</tr>
<tr>
<td>Anakinra</td>
<td>2</td>
</tr>
<tr>
<td>Abatacept</td>
<td>7</td>
</tr>
</tbody>
</table>
## Biologics in Early RA

**ASPIRE**

<table>
<thead>
<tr>
<th></th>
<th>MTX (%)</th>
<th>MTX + INF 3mg/kg (%)</th>
<th>MTX + INF 6 mg/kg (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACR70</td>
<td>21.2</td>
<td>32.5*</td>
<td>37.2*</td>
</tr>
<tr>
<td>DAS28 &lt;2.6</td>
<td>15</td>
<td>21.2</td>
<td>31.0*</td>
</tr>
<tr>
<td>≥ 1 serious infection</td>
<td>2.1</td>
<td>5.6*</td>
<td>5.0*</td>
</tr>
</tbody>
</table>

**COMET**

<table>
<thead>
<tr>
<th></th>
<th>MTX (%)</th>
<th>MTX + etanercept (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DAS28 &lt;2.6</td>
<td>28</td>
<td>50*</td>
</tr>
<tr>
<td>Non-progression</td>
<td>80</td>
<td>59*</td>
</tr>
<tr>
<td>Serious infection</td>
<td>3</td>
<td>2</td>
</tr>
</tbody>
</table>

**PREMIER**

<table>
<thead>
<tr>
<th></th>
<th>MTX (%)</th>
<th>MTX + adalimumab (%)</th>
<th>Adalimumab (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DAS28 &lt; 2.6</td>
<td>25</td>
<td>49**</td>
<td>25</td>
</tr>
<tr>
<td>Non-progression</td>
<td>34</td>
<td>61**</td>
<td>45*</td>
</tr>
<tr>
<td>Serious infections</td>
<td>1.6</td>
<td>2.9^</td>
<td>0.7</td>
</tr>
</tbody>
</table>

* p<0.05 compared to MTX, **p<0.05 compared to MTX and adalimumab, ^p<0.05 compared to adalimumab

## Biologics in Early RA

**AGREE** | MTX (%) | MTX + abatacept (%)
---|---|---
DAS28 < 2.6 | 23.3 | 41.4*  
Non-progression | 48.3 | 59.1*  
Serious infections | 2 | 2  
**AMBITION** | MTX (%) | Tocilizumab (%)
---|---|---
DAS28 < 2.6 | 12.1 | 33.6*  
Serious infection | 0.7 | 1.4  
* p<0.05 compared to MTX

## Biologics after TNF Failure

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Placebo (%)</th>
<th>Biologic (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Golimumab</td>
<td>ACR70</td>
<td>3</td>
</tr>
<tr>
<td>Abatacept</td>
<td>ACR70</td>
<td>1.5</td>
</tr>
<tr>
<td>Rituximab</td>
<td>ACR70</td>
<td>1</td>
</tr>
<tr>
<td>Tocilizumab</td>
<td>DAS &lt; 2.6</td>
<td>1.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* p<0.05 compared to placebo

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Boxed Warning

- Data supporting increased risk and no increased risk
  - Clinical trials may not be long enough or have enough patients
  - Meta-analysis use data from trials
  - Registries limited for many medications

<table>
<thead>
<tr>
<th>Medication</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adalimumab</td>
<td>1.12 (0.73-1.70)</td>
</tr>
<tr>
<td>Certolizumab</td>
<td>3.51 (1.59-7.79)</td>
</tr>
<tr>
<td>Etanercept</td>
<td>1.06 (0.74-1.51)</td>
</tr>
<tr>
<td>Golimumab</td>
<td>1.29 (0.71-2.35)</td>
</tr>
<tr>
<td>Infliximab</td>
<td>1.45 (0.99-2.13)</td>
</tr>
<tr>
<td>Abatacept</td>
<td>0.57 (0.3-1.08)</td>
</tr>
<tr>
<td>Anakinra</td>
<td>1.08 (0.47-2.50)</td>
</tr>
<tr>
<td>Rituximab</td>
<td>0.97 (0.64-1.48)</td>
</tr>
<tr>
<td>Tocilizumab</td>
<td>1.58 (0.85-2.94)</td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td><strong>1.19 (0.94-1.52)</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Risk</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt; 60 years old</td>
<td>1.6 (1.1-2.4)</td>
</tr>
<tr>
<td>Chronic lung disease</td>
<td>1.7 (1.1-2.6)</td>
</tr>
<tr>
<td>History of serious infection</td>
<td>2.1 (1.0-4.3)</td>
</tr>
<tr>
<td>Steroids 7.5-14 mg/day</td>
<td>2.1 (1.4-3.2)</td>
</tr>
<tr>
<td>Steroids &gt; 15 mg/day</td>
<td>4.7 (1.2-2.7)</td>
</tr>
<tr>
<td>Anti-TNF alpha</td>
<td>1.8 (1.2-2.7)</td>
</tr>
</tbody>
</table>

Tuberculosis

- Relative risk compared to etanercept
  - Adalimumab: 4.2 (1.4-12.4)
  - Infliximab: 3.1 (1.0-9.5)
- 7 fold increased risk if not screened properly

Risk factors for latent TB

- TB skin test
- AND Chest X-ray
- Further eval

- Repeat test if exposed
- TB skin test

Infections

**Histoplasmosis**
- 240 cases
  - Adalimumab: 16
  - Etanercept: 17
  - Infliximab: 207
- 21 cases-therapy delayed
  - 12 died

**Herpes Zoster**
- Adjusted risks
  - Infliximab and adalimumab
    - 1.82 (1.05-3.15)
  - Etanercept
    - 1.36 (0.73-2.55)
  - Steroids ≥ 10 mg/day
    - 2.52 (1.12-5.65)

Infection Management

- Increased risk with concomitant therapy
  - Do not use multiple biologics together

- Hold therapy for active infection
  - Resume after treated

- Postoperative infection risk
  - Hold at least 1 week prior and after

## Malignancy in RA

<table>
<thead>
<tr>
<th></th>
<th>SIR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall malignancies</td>
<td>1.05</td>
<td>1.01-1.09</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>2.08</td>
<td>1.80-2.39</td>
</tr>
<tr>
<td>Lung Cancer</td>
<td>1.63</td>
<td>1.43-1.87</td>
</tr>
<tr>
<td>Colorectal Cancer</td>
<td>0.77</td>
<td>0.65-0.90</td>
</tr>
<tr>
<td>Breast Cancer</td>
<td>0.84</td>
<td>0.79-0.90</td>
</tr>
</tbody>
</table>

Malignancy with Biologics

- FDA meta-analysis
  - Infliximab RR: 1.00 (0.67-1.43)
  - Adalimumab RR: 0.97 (0.77-1.20)
  - Etanercept RR: 0.86 (0.56-1.31)

- Swedish Biologics Register: anti-TNF treatment
  - Vs. anti-TNF naïve: 1.35 (0.82-2.11)
  - Vs. general population: 2.72 (1.82-4.08)

## Malignancy

<table>
<thead>
<tr>
<th>Medication</th>
<th>Lymphoma Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adalimumab</td>
<td>0.11 / 100 pt years</td>
</tr>
<tr>
<td>Certolizumab</td>
<td>3 / 2,367 patients</td>
</tr>
<tr>
<td>Etanercept</td>
<td>0.10 / 100 pt years</td>
</tr>
<tr>
<td>Golimumab</td>
<td>0.21 / 100 pt years</td>
</tr>
<tr>
<td>Infliximab</td>
<td>0.08 / 100 pt years</td>
</tr>
<tr>
<td>Abatacept</td>
<td>0.10 / 100 pt years</td>
</tr>
<tr>
<td>Anakinra</td>
<td>0.12 / 100 pt years</td>
</tr>
</tbody>
</table>
Tocilizumab

- **Elevated AST/ALT**

<table>
<thead>
<tr>
<th></th>
<th>AST</th>
<th>ALT</th>
</tr>
</thead>
<tbody>
<tr>
<td>ULN to 3 x ULN</td>
<td>22-41%</td>
<td>36-48%</td>
</tr>
<tr>
<td>3-5 x ULN</td>
<td>0.3-2%</td>
<td>1-5%</td>
</tr>
<tr>
<td>&gt;5 x ULN</td>
<td>0.1-0.7%</td>
<td>0.7-1.5%</td>
</tr>
</tbody>
</table>

- **Lipids**
  - LDL increased: 13-25 mg/dL

- **Hematologic**
  - Neutrophils <1,000/mm$^3$: 1.8-3.4%
  - Platelets <100,000/mm$^3$: 1.3-1.7%
BeST

- **Group 1:** Sequential monotherapy
  - MTX → SSZ → LEF

- **Group 2:** Step-up combination therapy
  - MTX → +SSZ → +HCQ →+prednisone

- **Group 3:** Initial combination with prednisone
  - MTX+SSZ+pred → MTX+CSA+pred → MTX + inflix

- **Group 4:** Initial combination with infliximab
  - MTX+inflix → SSZ → LEF

BeST-Clinical Results

# BeST-Radiographic Results

<table>
<thead>
<tr>
<th>Radiographic Progression – 2 yrs</th>
<th>Mean change</th>
<th>Median change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td>9.0</td>
<td>2.0</td>
</tr>
<tr>
<td>Group 2</td>
<td>5.2</td>
<td>2.0</td>
</tr>
<tr>
<td>Group 3</td>
<td>2.6</td>
<td>1.0</td>
</tr>
<tr>
<td>Group 4</td>
<td>2.5</td>
<td>1.0</td>
</tr>
</tbody>
</table>

### BeST-Adverse Effects

<table>
<thead>
<tr>
<th>Condition</th>
<th>Group 1 (%)</th>
<th>Group 2 (%)</th>
<th>Group 3 (%)</th>
<th>Group 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 1 AE</td>
<td>43</td>
<td>47</td>
<td>37</td>
<td>39</td>
</tr>
<tr>
<td>GI symptoms</td>
<td>16</td>
<td>15</td>
<td>8</td>
<td>11</td>
</tr>
<tr>
<td>Skin rash</td>
<td>10</td>
<td>12</td>
<td>9</td>
<td>6</td>
</tr>
<tr>
<td>Infections</td>
<td>4</td>
<td>7</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Cardiovascular events</td>
<td>2</td>
<td>2</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>Serious AE</td>
<td>6</td>
<td>7</td>
<td>13</td>
<td>5</td>
</tr>
</tbody>
</table>
BeST

- With intense monitoring and adjustments, all treatment strategies are effective

- Combination results in faster response
  - Infliximab and prednisone can be withdrawn

- Combination therapy results in less joint damage at 2 years

Phase I

MTX (SSZ, LEF, IM gold)

Poor Prognostic Features

Phase II

Yes

Anti-TNF

No

MTX, SSZ, LEF, IM gold

OR

Combination

Phase III

Change biologic:

Switch anti-TNF

Replace anti-TNF with abatacept, rituximab or tocilizumab

Current and Emerging Immunotherapy for Gastrointestinal Diseases

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Conflicts of Interest

- No conflicts to disclose.
Objectives

• Discuss the role of immunomodulation for Crohn's Disease (CD) and Ulcerative Colitis (UC)
• Identify short and long-term complications of immunomodulatory therapy used for gastrointestinal disorders
What Is Inflammatory bowel disease (IBD) ?

- Generic term for a series of chronic inflammatory conditions of the GI tract
- About 600,000 patients have some form of IBD in the US
- Wide spectrum of disease
  - Some patients are asymptomatic while others have severe, life threatening disease
- By convention most patients with IBD have either:
  - Ulcerative Colitis (UC)
    - Involving the large intestine only
  - Crohn’s Disease (CD)
    - Can involve any area of the GI Tract but ileocolonic disease is most common
Epidemiology

- Peaks between ages of 15 and 30 years
- European ancestry
- Urban greater than rural dwellers
- Whites greater than non-whites
- Occurs in familial clusters
  - 44% concordance among twins
- Genetics plays a role
  - NOD2 gene found to be associated with CD and worse outcomes

Pathogenesis

• The gut has its own mucosal immune system
  – Very fine-tuned to separate out foreign antigens (which it should attack) from nutrients (which it shouldn’t)

• Current theories are that some insult: Dietary? Infectious? triggers a gut immune system pro-inflammatory cascade that cannot be turned off by the system’s natural inhibitors
  – Dramatically increased production of cytokines in the gut (IL-1, TNF-α, IFN)

Treatment of Ulcerative Colitis

**Type of UC**

- Proctitis
- Mild-to-Moderate Distal UC
- Mild-to-Moderate Pancolitis
- Severe Pancolitis

**Induction of Remission**

- Topical 5-ASA
- 5-ASA Foam/Enema or oral 5-ASA
- Oral 5-ASA
- IV corticosteroids

**Maintenance Treatment**

- Topical 5-ASA
- 5-ASA Foam/Enema or oral 5-ASA
- Oral 5-ASA
- Inflammab or Surgery

**Refactory Treatment**

- Oral 5-ASA
- 5-ASA Foam/Enema or oral 5-ASA
- Oral 5-ASA
- Infliximab or Surgery

**Key:**

- UC = Ulcerative Colitis
- 5-ASA = Mesalamine
- Pancolitis = Extensive colitis
- 6MP = 6-mercaptopurine
- IV = Intravenous

Treatment of Crohn’s Disease

- Mild to Moderate Disease (Induction)
  - Budesonide or Corticosteroids
- Moderate to Severe Disease (Induction)
  - Corticosteroids or TNF Blocking drugs
- Maintenance Therapy for all types of CD
  - Start 6-MP/Azathioprine if moderate or severe symptoms or relapse occurs. MTX is an alternative therapy. If these agents (or infliximab) induced remission continue on those agents

Treatment of Crohn’s Disease

- **Fistulizing disease**
  - [TNF Agents](#) or Surgery
- **Fulminant Disease**
  - IV Corticosteroids or [Infliximab](#) or Surgery
- **Refractory Disease**
  - [Natalizumab](#) or Surgery

Role of Immune Modulating Drugs In IBD

• Ulcerative Colitis
  – Largely reserved for patients who are not candidates for surgery but 5-ASA strategies are ineffective

• Crohn’s Disease
  – More commonly used than in UC
  – Use primarily as a steroid-sparing strategy or in patients with refractory symptoms
  – Can be useful in Fistulizing disease

Azathioprine/6-Mercaptopurine

- Standard therapy for CD maintenance
- More rarely used for maintenance of UC
- Takes up to 3 months for full effectiveness
- Metabolism largely genetically determined
  - Multiple metabolites
  - Associated with ADRs especially leukopenia

AZA/6-MP Adverse Effects

- Pancreatitis = 3%
- Leukopenia = 2-10%
- Rash/allergic reaction = 2%
- Hepatitis = 1%
- Infectious = 7%
- Lymphoma
  - Slightly increased risk (4-fold, about 1/35,000)

AZA/6-MP Metabolism

Azathioprine

6-Mercaptopurine

TPMT

6-thioinosine 5’-monophosphate

TPMT

XANTHINE OXIDASE

6-thioguanine nucleotides

Efficacy and Leukopenia

Thiouric Acid

Liver Toxicity

6-Methyl-Mercaptopurine

Sandborn WJ. Dig Dis 2010;28:536–542
Pharmacogenomics of AZA/6-MP

• 10% of patients have poor TPMT activity
  – Responsible for 25-40% of episodes of leukopenia
• Patients with higher 6-Methyl-Mercaptopurine levels are at increased risk of hepatic toxicity
• Variable correlation of 6-thioguanine levels and efficacy
Is PGX Monitoring Effective?

• 207 IBD patients
  – TPMT activity and TGN levels measured at initiation of AZA/6-MP therapy and for 6 months after
  – TPMT metabolite status and TGN levels compared to clinical response and ADRs
  – Patients with either leukopenia or LFT abnormalities
    • 79% heterozygous vs. 35% wild-type TPMT, (P < 0.001)
  – Mean TGN levels > 100 ng/ml were more likely to have a successful clinical response

Biologics in IBD

• Infliximab and Adalimumab
  – Approved for UC and CD
  – Infliximab usually used first
  – Infliximab one of the few medical treatments for fistulizing disease

• Certolizumab
  – Pegylated TNF-α receptors
  – Approved for CD only
• Natalizumab
  – Humanized MoAb against the cellular adhesion molecule α4-integrin
  – Usually considered last line in CD due to risk of progressive multifocal leukoencephalopathy (PML)
  – 95 cases of PML and 20 deaths since 2007 (1.16 per 1000 patients treated)

How effective are TNF Blockers in IBD?

- Meta-Analysis of all three TNF blocking agents in IBD up to 2007
- 21 Studies with 5356 patients including luminal and fistulizing CD

Meta-Analysis Results

Both results $p < 0.001$, NNT for induction 7 and for remission 9
Where to Place TNF Blockers in CD Treatment

• SONIC study
  – 508 patients randomized to receive AZA, AZA + infliximab, or infliximab 5 mg/kg alone
  – Primary endpoint was the proportion of patients in steroid-free remission (CDAI < 150) at week 26
  – All patients allowed adjunctive medications except steroids
  – All patients received pharmacogenomic guided AZA dosing

SONIC Results

*AZA + INF vs INF p = 0.02, INF vs AZA p = 0.009

**AZA + INF vs INF p = 0.008, INF vs AZA p < 0.001
Loss of Response to Infliximab

• Several analyses have suggested up to 50% of patients lose response to standard doses of infliximab
• One narrative review suggested about a 13% per year loss of effectiveness
• Strategies to “recapture” patients
  – Intensify infliximab dosing regimen
  – Change to another TNF blocker

Human Anti-Chimeric antibodies (HACA)

- Development of HACA seems to be main factor associated with loss of infliximab effectiveness
- Factors associated with development of HACA
  - Episodic treatment
  - Lack of concomitant immunomodulator therapy
  - Low trough serum levels


Monitoring HACA and Trough Infliximab Levels

• Retrospective study from the Mayo group
  – 155 patients who had both HACA levels and trough infliximab levels measured
  – Roughly 75% of patients had partial or complete loss of response

• Looked at strategy and success of “recapturing” response
  – Switching to adalimumab
  – Increasing dose/Decreasing interval of infliximab

Response Rate (%)
Will New Strategies Prevent Loss of Response?

• Prevent HACA Development
  – Concomitant immunosuppressives
  – A single dose of hydrocortisone before infusion
  – Scheduled infusions

• Will dosing regimens guided by serum levels occur in the future?

Long term use of Adalimumab

- CHARM study
  - 56-week, phase III, R, PC trial
  - Moderate-to-severe CD
  - Primary outcome: Remission at 1 year, Open label extension looked at fistula closure
  - Open-label induction therapy for 4 weeks, then weekly or every other week therapy stratified by induction
  - At 120 weeks, 19/30 (63%) of patients remaining in the trial had fistula healing

CHARM Results

*p < 0.001
Antibodies to Other TNF- Blockers

- 3 year study in RA patients using adalimumab
- Prospective cohort study in 272 patients
- Baseline and periodic disease activity, Ab development and trough adalimumab levels assessed
  - 28% developed anti-adalimumab Ab
  - These patients had significantly lower trough adalimumab levels and had a higher risk of treatment failure (HR, 7.1; 95% CI, 2.1-23.4; P < .001) compared to patients without Ab

Safety of TNF Blockers

- Immunologic (0.001% to 1%)
  - Infusion reactions/site reactions
  - Serum sickness
  - Lupus like symptoms

Ferkolj I. J Physiol Pharmacol. 2009;60:67-70
Safety of TNF Blockers

• Malignancy
  – Hepatosplenic T-cell Lymphoma
    • A rare subtype of peripheral T-cell NHL
    • Roughly 20 cases reported since 2007
    • Reported in AZA treated patients alone but most commonly in patients on both AZA and Infliximab
    • Almost exclusively in young males
  – Increasing caution in this population

Safety of TNF Blockers

- **Lymphoma**
  - Long a controversial topic
  - TREAT registry with infliximab did not find an increase in risk
  - Recent meta-analysis did find a small increase in risk (6.1 per 10,000 patient-years)
  - Practice guidelines suggest a very slightly increase risk over other IBD treatments
  - Risk vs Benefit in informed patients

Safety of TNF Blockers

- **Infection**
  - Bacterial, fungal, opportunistic all increased
  - TREAT registry found a significant increase in opportunistic infections
    - Fungal
    - TB
    - Other
  - But no overall increase in serious infections
    - (OR, 0.99; 95% CI, .64-1.54)
  - Concomitant steroid use increases risk significantly
    - (OR, 2.21; 95% CI, 1.46-3.34)

Infliximab Failures: What Next?

- **WELCOME Study**
  - **OL study:** 539 patients with loss of response to infliximab
  - Patients randomized to standard induction with certolizumab 400 mg at weeks 0, 2, and 4, then continuation therapy
  - **Primary outcome:** Therapeutic response and remission
  - **Results:** 62% of patients demonstrated therapeutic response, 39% achieved remission

Emerging Therapies for IBD

- **Semapimod**
  - Found not to be effective in CD in a Phase II trial
- **Alicaforsen**
  - Antisense against ICAM-1 Failed to find benefit for CD
- **Ustekinumab**
  - Blocks the p40 subunit of IL-12 and 23
  - Small study suggested a benefit, but larger study did not substantiate this benefit in CD
Emerging Therapies In IBD

• AIN457
  – MAB against IL-17A undergoing Phase II testing for CD

• Golimumab
  – TNF Blocker in Phase III studies for CD

• Abtacept
  – Selective costimulation modulator of T-Cells undergoing Phase II Testing for CD
Bottom Line

- The “biologic” revolution in IBD has slowed considerably with any new drugs years away for use in either CD or UC
- Subtle differences in the immuno-pathology of diseases such as RA, SLE and IBD may explain the variable effect of biologics
- No major therapy advances expected soon
Conclusions

- Immunotherapy has transformed the treatment of IBD
- Although the exact timing of such therapy remains to be elucidated, expect more aggressive therapy with biologics sooner
- PGx, serum levels of immunotherapy may optimize therapy
- This plus the safety profiles of these medications dictate the participation of clinical pharmacists
Thank you

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