Assessing the Evolving Value of Rheumatoid Arthritis Therapies
Educational Objectives

• Assess decision support tools to enhance medical and pharmacy benefit design decision-making for patients with RA
• Interpret results of decision support tools with health plan affiliated rheumatology professionals to improve outcomes for patients with RA
• Employ specialty pharmacy and disease management services that can improve the quality of care for patients with RA
• Provide accurate and appropriate counsel as part of the managed care treatment team
Assessing the Clinical Benefits of Rheumatoid Arthritis Therapies in a Managed Care Setting

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UCLA David Geffen School of Medicine
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Learning Objective

- Review the clinical benefits of early and aggressive treatment of rheumatoid arthritis (RA)
RA Treatment Challenges

- Complex, multifactorial pathogenesis
- Fluctuating clinical course; unpredictable prognosis
- Characterized by
  - Progressive joint destruction
  - Loss of physical function
  - Poor quality of life

Progression of RA

- Inflammatory joint symptoms determine disability early in natural history of the disease
- Joint destruction dominates disability late in disease

RA Therapeutic Objectives

- Sustained remission
- Prevention/arrest of joint damage
- Prevention/reversal of disability
- Prevention of systemic comorbidities

Early and Intensive Treatment
Attenuate inflammation quickly

Treat-to-Target
Achieve remission with minimal/no signs or symptoms of active inflammation

Achieve Tight Control
Maintain remission or a low level of disease activity over time

Early and Aggressive Treatment Elicits Greater Disease Control

Disease Activity and DAS28 Remission at 52 Weeks (Data from the COMET Trial)

A higher proportion of patients with very early RA achieved low disease activity and remission when treated more aggressively.

Relationships:
- VERA; ETN + MTX (n = 263)
- VERA; MTX (n = 263)
- ERA; ETN + MTX (n = 263)
- ERA; MTX (n = 263)

Early and Aggressive Treatment Elicits Greater Disease Control

Randomized, double-blind, parallel treatment trial of MTX-naïve patients with moderate to severe early RA (n = 542)

Key Points:
- COMET=combination of methotrexate and etanercept in active early RA; DAS28=28-joint Disease Activity Score; DMARD=disease-modifying antirheumatic drug; ERA=early rheumatoid arthritis; ETN=etanercept; MTX=methotrexate; TNF=tumor necrosis factor; VERA=very early rheumatoid arthritis.
Treat-to-Target Elicited Remission in 65% of RA Patients

Data from the TICORA Study

- ACR20=American College of Rheumatology 20% improvement criteria
- ACR50=American College of Rheumatology 50% improvement criteria
- ACR70=American College of Rheumatology 70% improvement criteria
- TICORA=Tight Control for Rheumatoid Arthritis

*P < .0001 vs routine care
*Disease activity score < 1.6

Intention-to-treat population; n = 111 patients with RA duration < 5 years.

Treatment Intensification Achieves Remission More Often, Faster, and For a Longer Period of Time

Data from the CAMERA Study‡

<table>
<thead>
<tr>
<th></th>
<th>Conventional</th>
<th>Intensive</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Time to remission, mo.</strong></td>
<td>14.3</td>
<td>10.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><em>(95% CI)</em></td>
<td>(12.6 – 16.1)</td>
<td>(9.1 – 11.7)</td>
<td></td>
</tr>
<tr>
<td><strong>Duration of remission, mo.</strong></td>
<td>9.1</td>
<td>11.6</td>
<td>0.025</td>
</tr>
<tr>
<td><em>(95% CI)</em></td>
<td>(7.6 – 10.6)</td>
<td>(10.1 – 13.1)</td>
<td></td>
</tr>
<tr>
<td><strong>Median Area Under the Curve (IQ0.25-0.75)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morning stiffness</td>
<td>23.7</td>
<td>17.0</td>
<td>0.009</td>
</tr>
<tr>
<td><em>(95% CI)</em></td>
<td>(12.3 – 56.7)</td>
<td>(7.5 – 41.2)</td>
<td></td>
</tr>
<tr>
<td>ESR</td>
<td>21.6</td>
<td>17.7</td>
<td>0.007</td>
</tr>
<tr>
<td><em>(95% CI)</em></td>
<td>(13.0 – 33.6)</td>
<td>(10.2 – 27.6)</td>
<td></td>
</tr>
<tr>
<td>Tender joint count</td>
<td>5.5</td>
<td>3.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><em>(95% CI)</em></td>
<td>(2.8 – 9.2)</td>
<td>(1.9 – 6.0)</td>
<td></td>
</tr>
<tr>
<td>Swollen joint count</td>
<td>4.7</td>
<td>2.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><em>(95% CI)</em></td>
<td>(2.8 – 7.6)</td>
<td>(1.5 – 5.2)</td>
<td></td>
</tr>
</tbody>
</table>

‡Two-year, multicenter, open-label trial of intensive treatment with methotrexate (MTX0 vs conventional therapy. Patients in both groups received MTX (n=299). Patients in the intensive treatment group came to the outpatient clinic once every month; adjustment of the MTX dosage was tailored to the individual patient on the basis of predefined response criteria. Patients of the conventional strategy group came to the outpatient clinic once every three months; they were treated according to common practice.

Early Treatment with Intensive DMARD Therapy Slows Radiographic Progression

Radiographic Progression According to Early EULAR Response
(Data from the CAMERA Study)

EULAR=European League Against Rheumatism; SHS=Sharp van der Heijde score (median values)

Barriers to RA Disease Control

- Factors associated with no adjustment in RA therapy despite documented high or moderate disease activity

<table>
<thead>
<tr>
<th>Barriers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Irreversible joint damage</td>
</tr>
<tr>
<td>Patient-driven preference for current therapy</td>
</tr>
<tr>
<td>Non-inflammatory muscle pain</td>
</tr>
<tr>
<td>Insufficient time to assess effect of recently initiated RA therapy</td>
</tr>
<tr>
<td>Safety concerns</td>
</tr>
<tr>
<td>Presence of comorbid conditions</td>
</tr>
<tr>
<td>Resistant disease</td>
</tr>
</tbody>
</table>

Feasibility of Treat-to-Target Strategy in Clinical Practice

- Success is highly dependent on physician adherence to the strategy in the clinical setting\(^1\)
- Maksymowych et al observed that in 30% to 60% of clinic visits, therapy intensification was not implemented after documentation of moderate to high RA disease activity by any metric\(^2\)
- In nearly 70% of the cases, the primary reason for not following a treat-to-target approach was a belief that current treatment was “acceptable”\(^3\)

Measures of Disease Activity and Progression Guide Treatment Decisions

### Biomarkers of inflammation
- ESR and CRP are acute-phase response measures scored as normal or abnormal based on local laboratory standards.
- If results of at least 1 of these 2 tests are abnormal, patient should be scored as having an abnormal acute-phase response.

### Disease activity scales
- American College of Rheumatology 20% improvement criteria (ACR20)
- Disease Activity Score-28 (DAS28)
- Simplified Disease Activity Score (SDAI)
- Clinical Disease Activity Score (CDAI)
- Easy Rheumatoid Arthritis Measure (ERAM)
- Global Arthritis Scale (GAS)
- Routine Assessment of Patient Index Data 3 (RAPID3)

CRP=C-reactive protein; ESR=erythrocyte sedimentation rate.
### Instrument

<table>
<thead>
<tr>
<th>Instrument</th>
<th>Thresholds of Disease Activity</th>
</tr>
</thead>
</table>
| Patient Activity Scale (PAS) or PASII (range 0–10) | Remission: 0–0.25  
Low activity: >0.25–3.7  
Moderate activity: >3.7 to <8.0  
High activity: ≥8.0 |
| Routine Assessment of Patient Index Data 3 (RAPID3) (range 0–10) | Remission: 0–1.0  
Low activity: >1.0–2.0  
Moderate activity: >2.0–4.0  
High activity: >4.0–10 |
| Clinical Disease Activity Index (CDAI) (range 0–76.0) | Remission: ≤2.8  
Low activity: >2.8–10.0  
Moderate activity: >10.0–22.0  
High activity: >22 |
| Disease Activity Score (DAS) 28 erythrocyte sedimentation rate (ESR) (range 0–9.4) | Remission: <2.6  
Low activity: ≥2.6 to 3.2  
Moderate activity: ≥3.2 to #5.1  
High activity: >5.1 |
| Simplified Disease Activity Index (SDAI) (range 0–86.0) | Remission: ≤3.3  
Low activity: >3.3 to ≤11.0  
Moderate activity: >11.0 to ≤26  
High activity: >26 |

# Routine Objective Measurement of Disease Activity Associated with Remission

<table>
<thead>
<tr>
<th>Trial</th>
<th>Factors Associated With Remission</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>TICORA¹</td>
<td>• Intense treatment • Frequent assessments • Predetermined thresholds for escalation of therapies</td>
<td>10x higher rate of remission in patients receiving frequent objective assessment and intense therapy vs routine care</td>
</tr>
<tr>
<td>BeST²</td>
<td>• Frequent assessments • Early escalation to combination therapy</td>
<td>Greater number of patients receiving frequent objective assessment and early escalation of therapy achieved remission vs routine care</td>
</tr>
</tbody>
</table>

BeST = The Dutch Behandel Strategieen study; TICORA = tight control for rheumatoid arthritis study.

Treat-to-Target Algorithm

ACTIVE RA

MAIN TARGET

REMISSION

SUSTAINED REMISSION

ALTERNATIVE TARGET

LOW DISEASE ACTIVITY

SUSTAINED LOW DISEASE ACTIVITY

Adapt therapy according to disease activity

Adapt therapy if state is lost

Use a composite measure of disease activity every 1-3 months

Assess disease activity every 3-6 months

Adapt therapy according to disease activity

Adapt therapy if state is lost

Duration of therapeutic response varies

Long-term RA treatment often involves a sequence of different therapies

Optimal sequencing determined by disease activity, response to therapy, and drug mechanism of action

Pharmacologic Interventions

- **Corticosteroids**
  - Methylprednisolone
  - Prednisone
  - Prednisolone

- **Conventional DMARDs**
  - Azathioprine
  - Hydroxychloroquine
  - Leflunomide
  - Methotrexate
  - Sulfasalazine

- **Biologic DMARDs**
  - TNF inhibitors
  - IL-1 inhibitors
  - B-cell agents
  - T-cell agents
  - IL-6 inhibitors
  - JAK inhibitors

DMARD=disease modifying anti-rheumatic drugs; JAK=Janus Kinase inhibitor; TNF=Tumor Necrosis Factor.
# Corticosteroids

<table>
<thead>
<tr>
<th>Drug</th>
<th>Initial US Approval</th>
<th>Brand Name</th>
<th>Route of Administration</th>
<th>Mechanism of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prednisone</td>
<td>1955</td>
<td>Generic</td>
<td>Oral</td>
<td>Anti-inflammatory and immunomodulator</td>
</tr>
<tr>
<td>Prednisolone¹</td>
<td>1955</td>
<td>Orapred ODT®</td>
<td>Oral</td>
<td></td>
</tr>
<tr>
<td>Methylprednisolone²-⁴</td>
<td>1957</td>
<td>Medrol®</td>
<td>Oral</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Solu-Medrol®</td>
<td>IV infusion or IM injection (in office)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Depo-Medrol®</td>
<td>IA, IL, IM, or soft tissue injection (in office)</td>
<td></td>
</tr>
</tbody>
</table>

IA=Intraarticular; IL=Intralesional; IM=Intramuscular; IV=Intravenous; ODT=Orally disintegrating tablet.

# Nonbiologic Disease Modifying Antirheumatic Drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Initial US Approval</th>
<th>Brand Name</th>
<th>Route of Administration</th>
<th>Mechanism of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfasalazine[^1]</td>
<td>1950</td>
<td>Azulfidine®</td>
<td>Oral</td>
<td>Not well defined</td>
</tr>
<tr>
<td>Methotrexate[^2,3]</td>
<td>1953</td>
<td>Generic</td>
<td>Oral</td>
<td>Dihydrofolate acid reductase inhibitor</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Otrexup™</td>
<td>SC injection</td>
<td></td>
</tr>
<tr>
<td>Azathioprine[^5,6]</td>
<td>1968</td>
<td>Imuran®</td>
<td>Oral or IV infusion</td>
<td>Immunosuppressant</td>
</tr>
</tbody>
</table>

## Currently Available Biologic Agents Indicated for the Treatment of RA

<table>
<thead>
<tr>
<th>Drug</th>
<th>Initial US Approval</th>
<th>Brand Name</th>
<th>Route of Administration</th>
<th>Mechanism of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etanercept¹</td>
<td>1998</td>
<td>Enbrel®</td>
<td>SC injection</td>
<td>TNF inhibitor</td>
</tr>
<tr>
<td>Infliximab²</td>
<td>1998</td>
<td>Remicade®</td>
<td>IV infusion</td>
<td>TNF inhibitor</td>
</tr>
<tr>
<td>Anakinra³</td>
<td>2001</td>
<td>Kineret®</td>
<td>SC injection</td>
<td>IL-1 receptor inhibitor</td>
</tr>
<tr>
<td>Adalimumab⁴</td>
<td>2002</td>
<td>Humira®</td>
<td>SC injection</td>
<td>TNF inhibitor</td>
</tr>
<tr>
<td>Certolizumab pegol⁵</td>
<td>2008</td>
<td>Cimzia®</td>
<td>SC injection</td>
<td>TNF inhibitor</td>
</tr>
<tr>
<td>Golimumab⁶</td>
<td>2009</td>
<td>Simponi®</td>
<td>SC injection</td>
<td>TNF inhibitor</td>
</tr>
<tr>
<td>Rituximab⁷</td>
<td>1997</td>
<td>Rituxan®</td>
<td>IV infusion</td>
<td>B-cell agent (anti-CD20 antibody)</td>
</tr>
<tr>
<td>Abatacept⁸</td>
<td>2005</td>
<td>Orencia®</td>
<td>IV infusion or SC injection</td>
<td>T-cell agent (selective costimulator inhibitor)</td>
</tr>
<tr>
<td>Tocilizumab⁹</td>
<td>2010</td>
<td>Actemra®</td>
<td>IV infusion or SC injection</td>
<td>IL-6 inhibitor</td>
</tr>
<tr>
<td>Tofacitinib¹⁰</td>
<td>2012</td>
<td>Xeljanz®</td>
<td>Oral</td>
<td>JAK inhibitor</td>
</tr>
</tbody>
</table>

IL=interleukin; IV=intravenous; JAK=Janus kinase; SC=subcutaneous; TNF=tumor necrosis factor.

# Emerging RA Therapies

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism of Action</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baricitinib</td>
<td>JAK1/2 inhibitor</td>
<td>Phase 3</td>
</tr>
<tr>
<td>Filgotinib</td>
<td>JAK1 inhibitor</td>
<td>Phase 2</td>
</tr>
<tr>
<td>ABT-494</td>
<td>JAK1 inhibitor</td>
<td>Phase 3</td>
</tr>
<tr>
<td>Sarilumab</td>
<td>IL-6R antagonist</td>
<td>Phase 3</td>
</tr>
<tr>
<td>Sirukumab</td>
<td>IL-6 inhibitor</td>
<td>Phase 3</td>
</tr>
<tr>
<td>Vobarilizumab (ALX 0061)</td>
<td>IL-6R antagonist</td>
<td>Phase 2</td>
</tr>
<tr>
<td>Clazakizumab</td>
<td>IL-6 inhibitor</td>
<td>Phase 2</td>
</tr>
<tr>
<td>Denosumab</td>
<td>RANKL inhibitor</td>
<td>Phase 3</td>
</tr>
<tr>
<td>Mavrilimumab</td>
<td>GM-CSF antagonist</td>
<td>Phase 2</td>
</tr>
</tbody>
</table>

JAK=Janus kinase; IL=interleukin; RANKL, receptor activator of NF-κB ligand; GM-GSF=granulocyte–macrophage colony-stimulating factor.

### Summary

<table>
<thead>
<tr>
<th>Section</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Treatment Goals</strong></td>
<td>• Achieve remission, relieve symptoms, prevent joint and organ damage, improve physical function and well-being, and reduce long-term complications</td>
</tr>
</tbody>
</table>
| **Treatment Strategy**   | • Early and aggressive treatment  
                          • Treat-to-target (remission)  
                          • Achieve tight control through individualized therapy                                                                                       |
| **Measures of Disease Activity/Progression** | • Use validated measurements to guide treatment decision-making                                                                                   |
| **Pharmacologic Management** | • Long-term treatment often involves a sequence of different therapies  
                          • Optimal sequencing is determined by response, disease progression, and effects of therapies on disease pathways |
Current Practice Guidelines Review

Edmund Pezalla, MD, MPH

CEO
Enlightenment Bioconsulting
Hartford, CT
Learning Objective

- Discuss current evidence-based rheumatoid arthritis (RA) treatment guidelines
Evolution of the American College of Rheumatology (ACR) RA Treatment Recommendations

**2008**

- Recommendations for the use of nonbiologic and biologic DMARDs when starting or resuming therapy

**2012**

- Update of the 2008 recommendations, including switching drugs

**2015**

- Update of the 2012 recommendations including treat-to-target, tapering, discontinuation of therapy, use of biologics in patients with comorbidities

DMARDs=disease-modifying antirheumatic drugs.

### Principles Guiding the Treatment of RA

- **Focus on common or everyday patients**

- **Cost is a consideration in these recommendations**

- **Measure disease activity using an ACR-recommended measure in a majority of encounters for RA patients**

- **Routinely perform functional status assessment using a standardized, validated measure at least once per year and more frequently if disease in active disease**

- **If a patient has low RA disease activity or is in clinical remission, switching from one therapy to another should be considered only at the discretion of the treating physician in consultation with the patient**

- **A recommendation favoring one medication vs another means the preferred medication is the recommended first option. However, a nonfavored medication may still be a potential option under certain conditions.**

ACR=American College of Rheumatology; MTX=methotrexate.  
Current ACR Guidelines Provide Recommendations on Six Primary Topics

1. Treat-to-target approach, tapering, and discontinuing medications
2. Assess disease activity using validated tools/instruments
3. Employ intensive therapy in early (<6 mo) and established RA (>6 mo)
4. Use of biologics in high-risk RA patients with comorbidities
5. Vaccination of RA patients starting/receiving DMARDs or biologics
6. Screening for TB in patients starting/receiving biologics or tofacitinib

Treat-to-Target

Targets

- Low disease activity
- Remission
- Other appropriate targets selected by the clinician and patient

Functional Assessment

- Assessment using validated tools
- Conduct at least once per year and more often in active RA

Instruments to Assess RA Disease Activity

- Clinical Disease Activity Index (CDAI)
  - Range: 0 - 76
- Disease Activity Score based on 28 joint count (DAS28) or erythrocyte sedimentation rate (ESR)
  - Range: 0 – 9.4
- Patient Activity Scale (PAS) or PAS II
  - Range: 0 – 10
- Routine Assessment of Patient Index Data 3 (RAPID3)
  - Range: 0 - 10
- Simple Disease Activity Index (SDAI)
  - Range: 0 - 86

The specific tool used does not matter; it’s more important to routinely assess disease activity.

Recommended Treatment Algorithm for Early RA

Treat-to-Target

DMARD-naïve early RA

Low disease activity

Moderate or high disease activity

DMARD monotherapy†

Moderate or high disease activity*†

Combination traditional DMARDs*† or TNF inhibitor ± MTX*† or non-TNF biologic ± MTX*†

*Consider adding low-dose glucocorticoids in patients with moderate or high RA disease activity when starting DMARDs and in patients with DMARD or biologic failure; †Also consider short-term glucocorticoids (<3 months) for RA disease flares. Non-TNF biologics include abatacept, rituximab, or tocilizumab

### Recommendations for Patients with Established RA

<table>
<thead>
<tr>
<th>Recommendations for Patients with Established RA</th>
<th>Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1.</strong> Regardless of disease activity level, use a treat-to-target strategy</td>
<td>Moderate</td>
</tr>
<tr>
<td><strong>2.</strong> If disease activity is low, in patients who have never taken a DMARD, use DMARD monotherapy (MTX preferred) over a TNFi</td>
<td>Low</td>
</tr>
<tr>
<td><strong>3.</strong> If disease is moderate or high in patients who have never taken a DMARD</td>
<td>High Moderate</td>
</tr>
<tr>
<td>• Use DMARD monotherapy (MTX preferred) over tofacitinib</td>
<td></td>
</tr>
<tr>
<td>• Use DMARD monotherapy (MTX preferred) over combination DMARD therapy</td>
<td></td>
</tr>
<tr>
<td><strong>4.</strong> If disease activity remains moderate or high despite DMARD monotherapy, use combination traditional DMARDs or add a TNFi or a non-TNF biologic or tofacitinib (all choices with or without MTX) rather than continuing DMARD monotherapy alone</td>
<td>Moderate to Very Low</td>
</tr>
<tr>
<td><strong>5.</strong> If disease activity remains moderate or high despite TNFi therapy in patients who are currently not on DMARDs, add one or two DMARDs to TNFi therapy rather than continuing TNFi therapy alone</td>
<td>High</td>
</tr>
</tbody>
</table>

Blue and bolded = strong recommendation

## Recommendations for Patients with Established RA

<table>
<thead>
<tr>
<th>Recommendations for Patients with Established RA</th>
<th>Level of Evidence</th>
</tr>
</thead>
</table>
| **6.** If disease activity remains moderate or high despite use of a single TNFi:  
  • Use a non-TNF biologic, with or without MTX, over another TNFi with or without MTX  
  • Use a non-TNF biologic, with or without MTX, over tofacitinib with or without MTX | Low to Very Low Very Low |
| **7.** If disease activity remains moderate or high despite use of a single non-TNF biologic, use another non-TNF biologic, with or without MTX, over tofacitinib, with or without MTX | Very Low |
| **8.** If disease activity remains moderate or high despite use of multiple (2+) sequential TNFi therapies, first use a non-TNF biologic, with or without MTX, over another TNFi or tofacitinib (with or without MTX) | Very Low |
| **9.** If disease activity still remains moderate or high despite the use of multiple TNFi therapies, use tofacitinib, with or without MTX, over another TNFi, with or without MTX, if use of a non-TNF biologic is not an option | Low |
| **10.** If disease is moderate or high despite use of at least one TNFi and at least one non-TNF biologic:  
  • First use another TNF biologic, with or without MTX, over tofacitinib  
  • If disease activity remains moderate or high, use tofacitinib, with or without MTX, over another TNFi | Very Low Very Low |

### Recommendations for Patients with Established RA

<table>
<thead>
<tr>
<th>Recommendations for Patients with Established RA</th>
<th>Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>11. If disease activity remains moderate or high despite use of DMARDs, TNFi, or non-TNF biologic therapy, add short-term, low-dose glucocorticoid therapy</td>
<td>High to Moderate</td>
</tr>
<tr>
<td>12. If disease flares in patients on DMARDs, TNFi, or non-TNF biologic therapy, add short-term glucocorticoids at the lowest possible dose and the shortest possible duration</td>
<td>Very Low</td>
</tr>
<tr>
<td>13. If the patient is in remission:</td>
<td></td>
</tr>
<tr>
<td>• Taper DMARD therapy</td>
<td>Low</td>
</tr>
<tr>
<td>• Taper TNFi, non-TNF biologic, or tofacitinib (also see #15)</td>
<td>Moderate to Very Low</td>
</tr>
<tr>
<td>14. If disease activity is low:</td>
<td></td>
</tr>
<tr>
<td>• Continue DMARD therapy</td>
<td>Moderate</td>
</tr>
<tr>
<td>• Continue TNFi, non-TNF biologic, or tofacitinib rather than rather than discontinuing respective medication</td>
<td>High to Very Low</td>
</tr>
<tr>
<td>15. If the patient's disease is in remission, DO NOT discontinue all RA therapies</td>
<td>Very Low</td>
</tr>
</tbody>
</table>

Blue and bolded = strong recommendation

Recommended Treatment Algorithm for Established RA

Patient reaches target: Remission

- If the patient is in remission
  - Taper DMARD therapy
  - Taper TNF inhibitors, non-TNF biologics, or tofacitinib

Patient reaches target: Low Disease Activity

- If disease activity is low:
  - Continue DMARD therapy
  - Continue TNF inhibitors, non-TNF biologics, or tofacitinib rather than discontinuing respective medication

Patient does not reach target

- If disease activity remains moderate or high, continue on protocol to advanced therapy

# Recommendations for the Treatment of RA Patients with High-Risk Comorbidities (1 of 2)

<table>
<thead>
<tr>
<th>Comorbid Condition</th>
<th>Recommendation</th>
<th>Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Congestive Heart Failure (CHF)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHF</td>
<td>Use combination DMARDs or non-TNF biologics or tofacitinib over TNFi</td>
<td>Moderate to Very</td>
</tr>
<tr>
<td>CHF Worsening on Current TNFi Therapy</td>
<td>Use combination DMARDs or non-TNF biologics or tofacitinib over another TNFi</td>
<td>Very Low</td>
</tr>
<tr>
<td><strong>Hepatitis B</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Active hepatitis B infection and receiving/received effective treatment</td>
<td>Same recommendations as in patients without Hepatitis B</td>
<td>Very Low</td>
</tr>
<tr>
<td><strong>Hepatitis C</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatitis C infection and receiving/received effective antiviral treatment</td>
<td>Same recommendations as in patients without Hepatitis B</td>
<td>Very Low</td>
</tr>
<tr>
<td>Hepatitis C infection and not receiving or requiring effective antiviral treatment</td>
<td>Use DMARDs over TNFi</td>
<td>Very Low</td>
</tr>
</tbody>
</table>

*Blue and bolded = strong recommendation*

## Recommendations for the Treatment of RA Patients with High-Risk Comorbidities (2 of 2)

<table>
<thead>
<tr>
<th>Comorbid Condition</th>
<th>Recommendation</th>
<th>Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Past History of Treated or Untreated Malignancy</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Previously treated or untreated skin cancer (non-melanoma or melanoma) | Use DMARDs *over* biologics in melanoma  
Use DMARDs *over* tofacitinib in melanoma  
Use DMARDs *over* biologics in non-melanoma  
Use DMARDs *over* tofacitinib in non-melanoma | Very Low |
| Previously treated lymphoproliferative disorder | Use *rituximab over* TNFi | Very Low |
| Previously treated lymphoproliferative disorder | Use combination DMARD *or* abatacept or tocilizumab *over* TNFi | Very Low |
| Previously treated solid organ malignancy | Same recommendation as in patients without solid organ malignancy | Very Low |
| **Previous Serious Infection** | | |
| Previous serious infection | Use combination DMARD *over* TNFi  
Use abatacept *over* TNFi | Very Low |

*Blue and bolded = strong recommendation*

Caveats

• Current guidelines recommend employing multiple medications based on the patient’s disease severity and progression instead of considering patient-specific factors that predict response to treatment.

• Clinical guidelines consider the severity of the disease when deciding treatment, but do not include any prediction of drug efficacy.

Summary

• Current RA treatment guidelines emphasize
  • Treating-to-target in both early and established RA with the goal of achieving low disease activity or remission
  • Routinely assessing disease activity
  • Individualizing treatment
  • Treating patients with comorbid conditions
  • Tapering of therapy in patients in established remission
Analyzing the Available Data to Assess the Value of RA Treatment Options

Fadia Tohme-Shaya, PhD, MPH
Professor and Vice Chair for Academic Affairs
University of Maryland School of Pharmacy
Baltimore, MD
Learning Objectives

• Consider the economic outcomes and value of currently available therapy
• Evaluate the determinants of RA treatment value
• Understand the use of claim data in considering value
Burden of RA Extends Beyond the Joint

Ambulatory Care Events:
2.9 million ambulatory care visits each year

Comorbidity
5x higher CV disease event rate vs general population

Hospitalizations
>15,000 hospitalizations with RA listed as the principle diagnosis annually

Fatigue and Psychological Dysfunction
Up to 80% of patients report fatigue and an estimated 40% suffer depression

Reduced Life Expectancy
Mortality rate is 1.5 to 1.6-fold higher in RA patients vs general population

RA Significantly Impairs Ability to Work

Percent of Patients Who Missed Work

<table>
<thead>
<tr>
<th>% of Patients</th>
<th>RA Patients</th>
<th>Non-RA Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>67%</td>
<td>58%</td>
</tr>
</tbody>
</table>

Days of Work Missed Each Year

<table>
<thead>
<tr>
<th>Number of Work Days Missed</th>
<th>RA Patients</th>
<th>Non-RA Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>14</td>
<td>10</td>
</tr>
</tbody>
</table>

Retrospective analysis of employed individuals aged 18 to 65 using 1996–2006 US Medical Expenditure Panel Survey data.

Analysis of a commercially insured population made up of 1 million members, using integrated medical and pharmacy administrative claims data from 2008 to 2010.

Cost of RA Treatment Increases Over Time as Function Declines

Increased Medical Resource Utilization in Patients with High Disease Activity

Total Medical Resource Use over 6 Months

- Low Disease Activity: $4000
- High Disease Activity: $7900
- Remission: $5500

Determining the Value of RA Treatments

- Increases in the number and use of biologics make them an important target for economic evaluation

- Economic evaluation tools include
  - Cost-effectiveness analysis (CEA): Compares the cost and effectiveness of two or more treatments
  - Cost-utility analysis (CUA): Subtype of CEA that utilizes quality-adjusted life-years (QALY) as a measure of effectiveness
    - Primary outcome measure in CUA is the incremental cost-effectiveness ratio (ICER)
    - ICER describes the ratio of the additional costs of a treatment (vs an alternative) to QALYs gained

Biologics Do Not Appear to be Cost-effective as First-line Therapy

Data from the BeST Study

- Anti-TNF agents are less cost-effective vs conventional DMARDs for newly diagnosed, treatment-naïve patients\(^1,2\)

BeST=The Dutch Behandel Strategieen study.
ICERs Favor Conventional DMARDs as First-line Therapy

<table>
<thead>
<tr>
<th>Conventional DMARD vs</th>
<th>ICER ($/QALY)</th>
<th>Payer Perspective</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adalimumab</td>
<td></td>
<td>$63,281 to $382,982/QALY</td>
</tr>
<tr>
<td>Infliximab</td>
<td></td>
<td>$71,936 to $1,464,344/QALY</td>
</tr>
<tr>
<td>Etanercept</td>
<td></td>
<td>$110,389 to $175,721/QALY</td>
</tr>
<tr>
<td>TNF inhibitors (class)</td>
<td></td>
<td>$139,744</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Societal Perspective</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infliximab</td>
</tr>
<tr>
<td>TNF inhibitors (class)</td>
</tr>
</tbody>
</table>

- These (and similar) findings lead most payers to require a trial of conventional DMARDs in treatment-naïve patients

Biologics Begin to Be Cost-effective After Failure of a Conventional DMARD

- Early treatment should be with nonbiologic therapies
- Biologic treatments become cost effective after failure of therapy a conventional DMARD

Mean 1-Year Biologic Cost Per Effectively Treated Patient

Analysis of a Commercial Claims Database

- Effective treatment defined as meeting all 6 of the following criteria: 1) medication possession ratio ≥80% for SC biologics, or at least as many infusions as specified in the label for IV biologics; 2) no increase in biologic dose; 3) no switch in biologics; 4) no new nonbiologic DMARD; 5) no new or increased oral glucocorticoid treatment; and 6) no more than 1 glucocorticoid injection.

- Analysis of 5,474 RA patients (18-63 years) in the Optum Research Database who initiated biologic treatment between January 2007 - December 2010 and were continuously enrolled 6 months before through 12 months after the first claim for the biologic agent.

ICERs Favor Treatment with Biologics in DMARD-inadequate Responders

<table>
<thead>
<tr>
<th>Sequential use/switching to another DMARD vs</th>
<th>ICER ($/QALY)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tocilizumab</td>
<td>$29,654/QALY</td>
</tr>
<tr>
<td>Abatacept</td>
<td>$58,376/QALY</td>
</tr>
<tr>
<td>Etanercept</td>
<td>$32,465 to $154,057/QALY</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>$33,96 to $317,650/QALY</td>
</tr>
<tr>
<td>Infliximab</td>
<td>$37,225 to $313,144/QALY</td>
</tr>
<tr>
<td>TNFa inhibitors (class)</td>
<td>$53,802 to $291,531/QALY</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Societal Perspective</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Infliximab</td>
<td>$59,924/QALY</td>
</tr>
<tr>
<td>Etanercept</td>
<td>$25,727 and $76,089/QALY</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>$34,183/QALY</td>
</tr>
<tr>
<td>Tocilizumab</td>
<td>$29,707/QALY</td>
</tr>
</tbody>
</table>

Cost-effective Strategy in the Treatment of TNF Inhibitor IR Patients

- TNF inhibitors are frequently used sequentially in the case of a patient experiencing an inadequate response (IR) or intolerance to another TNF inhibitor
- Switching between biologic agents is common in medical practice
  - However, there is limited evidence that compares the overall costs and effectiveness of such a strategy

1st Line Use of Tofacitinib in Moderate-to-Severe RA Appears to be Cost-effective

- Cost-effectiveness evaluation of the JAK inhibitor tofacitinib for the treatment of Korean patients with RA who had an inadequate response to conventional DMARDs
- 1st line use of tofacitinib increased QALY gained vs standard-of-care, resulting in an ICER of KRW 13,228,910 (~$12,000) per QALY
- JAK inhibitor use also increased QALYs when incorporated as a 2nd, 3rd, or 4th line therapy
- Sensitivity analyses yielded ICERs in the range of KRW 6,995,719 (~$6,000) per QALY to KRW 37,450,109 (~$33,000) per QALY
- An increase in overall cost was observed in patients receiving a JAK inhibitor (attributable to increased lifetime drug costs)
- From a societal perspective, the inclusion of an oral JAK inhibitor as a treatment strategy for moderate-to-severe RA is cost-effective

KRW = Korean won (1 KRW = 0.00089 USD)

Summary

- RA is associated with a significant clinical, psychosocial, and economic burden.
- Conventional DMARDs are a more cost-effective first line treatment strategy than TNF inhibitors.
- Treatment with a TNF inhibitors in patients refractory to previous DMARD therapies is more cost-effective vs switching to another conventional DMARD.
- In TNF-IR patients, the alternative (non-TNF) biologics appear to be more cost-effective than switching to another anti-TNF agent.
- Treatment with an oral JAK inhibitor for moderate-to-severe RA appears to be cost-effective across the treatment sequence.
Rheumatoid Arthritis
Comparative Analyses for Evidence-based Treatment and Benefit Design Decision-Making

Steven G. Avey, MS, RPh, FAMCP
Vice President, Specialty Clinical Programs
Medimpact Healthcare Systems, Inc.
San Diego, CA
In my lifetime…

Graduated from pharmacy school in 1976

What was the standard therapy for RA?
Drug of Choice for RA in 1976

Cost of therapy - Patient paid 100% = $50 to $100 per year
What did we do when patients had a GI Bleed?

No problem...
We put them on an antacid

2 tablespoonsful every 4 hours

Patients purchased Maalox by the case!
The World Has Changed
Agenda for 2016 RA Therapy

• New world / new therapies / new costs
• Real-world evidence
• Formulary decisions
• Contracting issues
• Where we go from here
Emergence of the Payer in the Decision-Chain

- Evidence Demands
  - Clinical Effectiveness
  - Safety
  - Population Safety/Long-term Safety
  - Cost
  - Total Cost of Care Impact

- Industry
- FDA
- Government
- Physician
- Employers/Exchanges
- Health Plan
- Patient

To Innovate
To Approve
To Pay for
To Prescribe
To Adhere

Shifting Landscape
Emerging Approach – Value Based

- RCTs
- Comparative data
- Real world data & modelling
- Various

- CLINICAL EFFICACY & SAFETY
- ADDED THERAPEUTIC VALUE
- HEALTH SYSTEM VALUE
- SOCIETAL VALUE

Complexity of data to demonstrate value
CER – Value in EBM Review of Medications

- Supports EBM approach
- Addresses key questions that formulary decision-makers need to consider regarding a medication
- Builds a foundation in developing a comprehensive EBM formulary drug review
- Tackles challenges in:
  - Reviewing and critically appraising large amounts of data
  - Analyzing several products in a class or across classes
- Identifies evidence gaps for future research
- Provides information for practical considerations
EBM Approach for Formulary Drug Review

What Information is Used?

**Trusted Sources - CER Systematic Reviews**
- Cochrane Database of Systematic Reviews
- Agency for Healthcare Research & Quality (AHRQ)
- Drug Effectiveness Review Project (DERP)
- Centre for Reviews and Dissemination
- Database of Abstracts of Reviews of Effects

**Trusted Sources are best known for:**
- Rigorous, systematic methodology
- Transparency
- Auditing/critical appraisal of included research to base conclusions
- Systematic reviews that hold up to critical appraisal by external users

“CER Systematic Reviews are NOT just narrative reviews.”
Formulary Drug Review
EBM Approach – Systematic Search

Key Questions (Formulary Issues)?

Scientific Information (Clinical Trials)

Evidence Quality

Evidence Synthesis

Superior

Inferior

Insufficient Evidence
(80 – 90% of drugs reviewed)

P & T Formulary Decisions
EBM Formulary Decisions
Transparency in Weighing Practical Considerations

- **Scientific Evidence**
  - High Confidence
  - Low Confidence

- **Superior vs Similar**

- **Practical Considerations***
  - Other Options
  - Safety Signals/Harms
  - Disease Characteristics
  - Standard of Care
  - Impact on Clinical Burden
  - Cost

* May include real-world research

Greatest Weight (Factor) = Scientific Data
EBM Formulary Drug Review
Practical Use of CER to Address Evidence Gaps

Key Questions (Formulary Issues)?

Scientific Information

Critical Appraisal

Evidence Quality

Evidence Synthesis

Superior

Can’t Tell Difference

Inferior

Evidence Gap

Greatest Weight (Factor) = Scientific Data

P & T Decisions

- Evidence
- Practical Considerations

CER

Real World → Prospective, Retrospective, Observations, Patient Registries, Claims Analysis
CER Application – Impact on Clinical Burden
Medication Persistence

CER Application: Outcomes/Overall Cost
Rheumatologic Biologics

Clinical Trial Data
• Reliable quality evidence for biologics in rheumatologic conditions (rheumatoid arthritis, psoriatic arthritis/psoriasis, ankylosing spondylitis)
• Compared to standard treatments (ie, with or without methotrexate)
• Limited evidence for direct head-to-head comparison

Real-world CER
Compared to Drug A for rheumatologic conditions, Drugs B or C associated with:
• Fewer % outpatient hospital, ER visits
• Lower monthly medical costs per utilizing member
• Lower overall monthly costs per utilizing member (medical/drug/administration costs)
The Future of Value Calculations

- Reduction in total medical costs
- Improvement in health status
- Quality Adjusted Life Year (QALY) – at what cost?
- Improvement in mortality
- Improvement in productivity
- Improvement in health status

QALY – at what cost?
Contracting and Evidence Issues

- Treatment failures
- Adherence failures
- Member failures
- Data and post marketing analyses
Reporting for Risk Sharing

**Side Effects and Exacerbation Events - 4Q**

- Bladder Symptoms
- Bowel Symptoms
- Depression
- Inj Site Reaction
- Ataxia
- Memory Symptoms
- Pain
- Sensory Symptoms
- Sexual Symptoms
- Spasticity
- Tremors

*Number of Patients*

- PhRMA commonly gets these reports
- We have a baseline from RCT data
- Compare 12 month data after product is approved

Such reports are available through an SP.
Risk-Sharing with an SP – Adherence

• Patients segmented for adherence by multiple parameters

• Target opportunities for adherence interventions

• Drill down on differences in adherence due to prescriber, drug, age, reported reasons for non-adherence, etc
New Risk-sharing for the Member

Adherence Contracts

- On the rise
- Increases member responsibility
- What happens with patients who are < 50% adherent?
- Advantages vs disadvantages
• Does post-marketing analysis compare to clinical trial data? Penalty or refund?
• Patient outcomes data will be required and agreed to
• Contracts already in place for adherence risk adjustment
Where Can We Go from Here?

- Determine better testing and outcomes assessments to determine patient health status
- Showcase advantages of treatment
- Better outcomes reporting on interventions and patient satisfaction
- Better collaboration between the PBM, the Specialty Pharmacy, and PhRMA