Individualizing Therapy in the Management of Rheumatoid Arthritis: A Closer Look at Emerging Therapeutic Options

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Learning Objectives
Overview

- Rheumatoid Arthritis (RA) overview
  - Clinical Consequences
  - Economic Overview of RA
  - RA Biologics as a Driver of Pharmacy Cost and Payer Issues
- Changing guidelines drive treatment paradigms as more therapeutic options become available
- Non-TNF therapeutic options for RA management
  - A focus on the JAK inhibitors
  - New evidence on what to use when a TNF fails
- Payer management of the RA category
  - A case for CER
  - Questions and Discussion

RA Background

Clinical Overview, Demographics and Economic Factors
Burden of Rheumatoid Arthritis

- **Definition:** Chronic, progressive, inflammatory, autoimmune disease of unknown etiology
- **Prevalence:** ~1.3 million Americans (0.6% of the US population)\(^1\)
- **Disability:** Many patients unable to work within 10 years of onset:
  - Pre-biologic era: 50%\(^2\)
  - Current (2008): 35%\(^3\)
- **Cardiovascular (CV) risk:** 5x higher CV event rate vs general population\(^4\)
- **Excess deaths:** Mortality rate 1.5 to 1.6-fold higher in RA patients vs general population\(^5\)


RA May Have Devastating Clinical Consequences

**Goals of Therapy:**
- Major goal is remission
- Alternative: lowering of disease activity
- Remission:\(^1\)
  - Complete absence of clinical signs and symptoms of synovitis
  - Elimination silent synovial inflammation
  - Normalization of acute phase reactants
- The concept of “Treat-to-Target” (T2T) and more structured approaches were put forth in 2012 and continued in 2015\(^2,3\)

2. Singh et al; Arthritis Care Res; 2012;64: 625-639
The Medical Cost of RA is Difficult to Measure

- Several studies have been done over the last decade to determine the direct medical cost of RA.
- However, these studies have produced a wide range of results.
  - One study published in 2004 estimated direct medical costs in the U.S. ranging from $2,298 to $13,549 per patient.¹
  - Data from studies between 2007 and 2012 have estimated that the per patient annual direct medical costs of RA range from $2,000 to $10,000, with estimated indirect costs ranging from $1,500 to $22,000.²³⁴


Drugs for RA are in the #1 Specialty Class

- We know that the economic burden of RA has grown substantially since the biologic therapies were first introduced in the mid to late 1990s.
- Most payers now report that the biologic drugs to treat RA (and other conditions) are among the top 5 drug categories by total cost and the number 1 specialty category*
Cost per Treated Patient

- In a 2015 paper, Curtis et al used a claims-based algorithm to estimate mean 1-year biologic cost per effectively treated patient. The authors reported the following costs:5
  - etanercept ($43,935)
  - golimumab ($49,589)
  - adalimumab ($52,752)
  - abatacept ($62,300)
  - infliximab ($101,402)


ICER: April 2017 Report

- Just released their report on Targeted Immunomodulator (TIM) class in April 2017
- "Acceptable range" in U.S. is $50-150,000
- Wide range in cost effectiveness of the TIMs for RA
- Currently this information does not drive drug selection
- However, this analysis was not based on net cost to payers

Changing RA Management Paradigms

- Treat Early and Aggressively
- Use Standardized Measurements

RA Management Challenges!

- No standardized outcome measures typically are used in clinical practice
- Growing number of biologic agents for the treatment of RA
  - Not every biologic agent works for every RA patient
  - Little understanding of the cause of variation of drug efficacy between patients
- Guidelines on how biologics should be compared to optimize RA treatment outcomes are lacking
  - Importance of understanding the optimal use of these agents magnified by their high cost
- Physicians, patients, and plan managers need better data to compare the effectiveness of the different biologics
- Caution when comparing drugs across studies

Therapeutic Window of Opportunity in Early RA

50%–70% of patients have radiographic damage within the first 2 years after onset of symptoms

Evolving RA Treatment Paradigm

Historical Approach

Past Approach 2012 Paradigm

2012 Guidelines were the first to change the paradigm

- Early aggressive treatment
- Biologics earlier in therapy
- Combination therapy
- Minimal disease activity

Initial treatment with Non-biologic DMARDs, Then escalate

Treat-to-Target Approach

- Key Elements
  - Monitor disease activity every 1-3 months until target is reached; then every 3-6 months
  - Adjust therapy regularly until goal is achieved
  - Aim at predefined target
- Goal
  - Remission
  - Low disease activity is acceptable alternative goal


2015 ACR Guidelines: Overview of Treat to Target

- Note treat to target approach is integral
- Multiple disease activity measurement points
- Goal is low or no disease activity
ACR Recommended Tools to Meet Treat-to-Target Goals

- Patient only tools
  - Patient activity scale (PAS or PAS-II)
  - Routine assessment of patient index data 3 (RAPID-3)
- Patient and provider tools
  - Clinical disease activity index (CDAI)
- Patient, provider, and lab data tools
  - DAS 28 ESR/DAS 28 CRP
  - Simplified disease activity index (SDAI)


Treat to Target Approach Vs Standard of Care

2015 ACR Guidelines Changed Treatment Approaches

- Some of the important aspects include:
  - Strong recommendation about treat to target
  - Emphasis on vaccination of the immunomodulated patient
  - For patients with moderate to high disease activity, consider adding low-dose glucocorticoids.
  - Short-term glucocorticoids can also be used for rheumatoid arthritis flares.
  - Tofacitinib appears for the first time


2015 ACR Guidelines Changed Treatment Approaches

- Managing more aggressively is now the approach:
  - For DMARD-naive patients with established disease:
    - DMARD monotherapy, usually methotrexate, is recommended first-line treatment for those with low, moderate, or high disease activity.
  - After MTX failure:
    - Combination of traditional DMARDs
    - TNF inhibitor with or without methotrexate
    - Non-TNF-inhibitor biologic with or without methotrexate
    - Tofacitinib plus methotrexate

2015 ACR Guidelines: More Therapeutic Options

Note that choices of agents now go beyond anti-TNFs in moderate to high disease activity and include non-TNF biologics and tofacitinib.

Summarizing the Core Principles in RA Clinical Management

- Diagnose early
- Start treatment immediately
- Treat to target is the goal
- Maintain tight control throughout the disease course
- Aim for remission if at all possible
- Individualize treatment
- Adjust treatment if target is not achieved

Therapeutic Options in RA

TNF Biologics: Therapeutic Mainstays

Pediatrics, July 2016. http://pediatrics.aappublications.org/content/early/2016/07/14/peds.2016-1209.figures-only
## Characteristics of Selected RA Biologics

<table>
<thead>
<tr>
<th>Target</th>
<th>Etanercept</th>
<th>Infliximab</th>
<th>Certolizumab</th>
<th>Adalimumab</th>
<th>Tocilizumab</th>
<th>Abatacept</th>
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<td>Enbrel</td>
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<td>TNF</td>
<td>TNF</td>
<td>TNF</td>
<td>IL-6 Inhibitor</td>
<td>T-Cell Modulation</td>
<td>B-Cell</td>
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<td>Half Life</td>
<td>3-5 Days</td>
<td>8-10 Days</td>
<td>14 Days</td>
<td>10-20 Days</td>
<td>8-14 days</td>
<td>13-16 Days</td>
<td>19 Days</td>
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<tr>
<td>Construct</td>
<td>Human</td>
<td>Chimeric</td>
<td>FAB-Pegylated</td>
<td>Human</td>
<td>Humanized (Mouse)</td>
<td>Human</td>
<td>Chimeric</td>
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<tr>
<td>Dosing</td>
<td>Once Biweekly-weekly</td>
<td>Once every 4-8 weeks</td>
<td>Once every 4-8 weeks</td>
<td>Once every 1-2 weeks</td>
<td>Once every 4-6 weeks</td>
<td>Once Monthly</td>
<td>Twice every 6-12 months</td>
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<tr>
<td>Route</td>
<td>Sub-Cut</td>
<td>I.V.</td>
<td>Sub-Cut</td>
<td>Sub-Cut</td>
<td>I.V.</td>
<td>I.V.</td>
<td>I.V.</td>
</tr>
</tbody>
</table>

### JAK Inhibitor-Tofacitinib

- Tofacitinib is an inhibitor of the enzymes janus kinase 1 (JAK1) and janus kinase 3 (JAK 3),
- Interferes with the JAK-STAT signaling pathway
- Prevents transmission of extracellular information into the cell nucleus, influencing DNA transcription
Tofacitinib Clinical Evidence Summary

- **Tofacitinib (2012)** FDA approved for the treatment of adults with moderately-to-severely active RA who have had an inadequate response to, or who are intolerant of, MTX.

- The FDA approved tofacitinib with a Risk Evaluation and Mitigation Strategy (REMS),
  - Consists of a medication guide advising patients about important safety information and a communication plan to inform health care providers about the serious risks associated with tofacitinib.
Tofacitinib: Safety Issues

- Warnings and Precautions include:
  - Gastrointestinal perforations - Use with caution in patients that may be at increased risk.
  - Laboratory monitoring - Recommended due to potential changes in lymphocytes, neutrophils, hemoglobin, liver enzymes and lipids.
  - Immunizations - Live vaccines should not be given concurrently with tofacitinib.
  - Severe hepatic impairment - Not recommended.
  - Serious infections - The most common serious infections reported with tofacitinib included pneumonia, cellulitis, herpes zoster, urinary tract infection, and diverticulitis. Avoid use of tofacitinib in patients with an active, serious infection, including localized infections.
  - Viral reactivation - Screening for viral hepatitis should be performed in accordance with clinical guidelines before starting tofacitinib.

New Evidence: JAMA September 2016

- Premise: One-third of patients with rheumatoid arthritis show inadequate response to tumor necrosis factor α (TNF-α) inhibitors; little guidance on choosing the next treatment exists.
- A total of 300 patients (conducted between 2009-2012)
  - Persistent disease activity (disease activity score in 28 joints–erythrocyte sedimentation rate [DAS28-ESR] ≥ 3.2 [range, 0-9.3])
  - Insufficient response to anti-TNF therapy
  - 52-week multicenter, pragmatic, open-label randomized clinical trial.
- Final follow-up date was in August 2013.
- Patients were randomly assigned (1:1) to receive a non–TNF-targeted biologic agent or an anti-TNF that differed from their previous treatment.
  - The choice of the biologic prescribed within each randomized group was left to the treating clinician.

Conclusions:

- **Findings:** In this randomized clinical trial involving 300 adults, 69% of patients achieved an effective clinical response with a non-TNF biologic vs 52% of patients who took a second anti-TNF drug.

- **Meaning** For patients with rheumatoid arthritis and an insufficient response to anti-TNF therapy, a non-TNF biologic agent may be more effective than a second TNF. 


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**Payer Management Challenges**

**RA Treatments**

What are some of the issues?
RA Treatment is Changing

- Rheumatologists are trying to meet aggressive treatment approaches to achieve early remission.
- Various combinations are being used.
- Biologics are being used more frequently and earlier in the treatment of RA.
- Treatments are going to be more frequently switched due to inadequate response or intolerance.


Drug and Disease Cost Issues

Drug costs are a payer challenge
- The immunomodulators are typically the number one drug spend for specialty (slide 9).
- Drug acquisition cost is high for the biologics for RA.
- Price increases have been another driver of cost.
- The pipeline in RA is robust and new entrants may drive additional cost.
- RA is a chronic disease—drug costs continue over years.

Total cost of care is difficult to assess
- It is often difficult for payers to merge medical and pharmacy data into a clear picture of total cost, especially in pharmacy benefit carve out situations.
- Benefit design changes and changes of carriers can make it hard to track cost year over year.
- The medical claims system often does not have granular information to allow care costs to be accurately tracked.
What are the Right Treatment Choices?

- Despite guideline recommendations, none of the standardized outcomes measures are typically used in clinical practice.
- Not every biologic agent works for every RA patient.
- Little understanding of the cause of variation of drug efficacy between patients.
- Guidelines on how biologics should be compared to optimize RA treatment outcomes are lacking.
  - Importance of understanding the optimal use of these agents magnified by their high cost.
- Physicians, patients, and plan managers need better data to compare the effectiveness of the different biologics.
  - Payers must use caution when comparing drugs across studies—but it is often the only method available.


Multiple Levels of Assessment are Required

**CAN IT WORK?**
- Randomized Controlled Trials

**DOES IT WORK?**
- Accumulated Evidence
- Clinical Guidelines Treatment Pathways

**IS IT WORTH IT?**
- Comparative Effectiveness Research
- Health Economics Research

**Informed Decision Making**
- Benefit Design Formulary Positioning Coverage Decisions

AHRQ CER Review of RA Therapies

- The 2011 analysis included 258 published articles reporting on 211 studies:
  - 31 head-to-head RCTs
  - 1 head-to-head non-RCT
  - 44 placebo controlled trials
  - 28 meta-analyses or systematic reviews
  - 107 observational studies
  - 30 studies for quantitative synthesis for analysis of effects on disease activity and joint damage
  - 42 studies for quantitative syntheses for analysis of adverse events


AHRQ’s CER Review of RA Therapies: Questions Addressed

- Do drug therapies differ in their ability to reduce disease activity, to slow or limit the progression of radiographic joint damage, or to maintain remission?
- Do drug therapies differ in their ability to improve patient-reported symptoms, functional capacity, or quality of life?
- Do drug therapies differ in harms, tolerability, patient adherence, or adverse effects?
- What are the comparative benefits and harms of drug therapies for RA in subgroups of patients:
  - stage of disease
  - prior therapy,
  - demographics,
  - concomitant therapies
  - comorbidities


4/14/2017
AHRQ's CER Review of RA Therapies: Summary of Findings

Comparisons of synthetic DMARDs revealed no significant differences in:

- Long-term clinical and radiographic outcomes
- Functional capacity
- Health-related quality of life
- Rates of adverse events

Biologic monotherapy vs combination therapy (biologic + MTX)
- Combination therapies were generally associated with better clinical response rates and outcomes


ICER: Value-Based Benchmarks

ICER's value-based price benchmark is comprised of two components: a range associated with the prices needed to achieve long-term cost-effectiveness; and the price at which the potential short-term budget impact could be so substantial that policymakers should consider whether special coverage, pricing, or payment mechanisms are needed to assure substantial access to high-value care for all patients.

Current Practice May Be Suboptimal

- A “start low, go slow” approach remains common in RA management\(^1\)
- Delayed treatment or prolonged under-treatment contributes to uncontrolled inflammation and irreversible tissue damage\(^2\)
- Patients not referred to a rheumatologist are less likely to receive disease-modifying anti-rheumatic drug (DMARD)-based therapy within 12 months of symptom onset\(^3\)
- Patients frequently receive irregular follow-up and minimal therapeutic adjustment\(^4\)

Summary

- RA is a chronic and costly disease from a payer perspective
- Drug treatment of RA is a major driver of specialty pharmacy cost
- Treatment approaches are changing and guidelines are moving towards earlier and more aggressive treatment
- Yet, current treatment often is sub optimal
- Payers are challenged to get the most value from RA treatments

Looking Ahead!

Pipeline and other considerations?
Monitoring Disease State Activity Will be More Important

- Currently there is a heavy reliance on clinical and patient driven evaluations.
- No tool to prospectively determine which therapy will benefit which patient
- Minimal ability to measure disease activity by labs due to non-specific markers of disease activity.
- Better measurements are needed.

Monitoring Disease State Activity

- One example: Multiple biomarker assay has potential

- Measuring B-cell activity may be another method*
  - Memory B cells secrete molecules called anti-citrullinated protein antibodies (ACPAs).
  - ACPA levels were directly proportional to the recirculating memory B cells in the blood stream

*Arthritis & Rheumatology, 2017; DOI: 10.1002/art.40053
RA Pipeline 2017 and Beyond

<table>
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<tr>
<th>Product</th>
<th>Indication(s)</th>
<th>MOA</th>
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<tbody>
<tr>
<td>baricitinib</td>
<td>Rheumatoid Arthritis</td>
<td>JAK Inhibitor (oral)</td>
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<tr>
<td>sirukumab</td>
<td>Rheumatoid Arthritis/Temporal</td>
<td>IL-6 Monoclonal Antibody</td>
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<td>Rheumatoid Arthritis</td>
<td>IL-6 Receptor Antibody</td>
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<tr>
<td>clazakizumab</td>
<td>Rheumatoid Arthritis/PsA</td>
<td>IL-6 Inhibitor</td>
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<td>mavrilimumab</td>
<td>Rheumatoid Arthritis</td>
<td>Monoclonal antibody to alpha subunit of GMCSF</td>
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<td>Rheumatoid Arthritis</td>
<td>Nano-antibody targeting IL-6R</td>
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<tr>
<td>filgotinib</td>
<td>Rheumatoid Arthritis</td>
<td>JAK Inhibitor (oral)</td>
</tr>
</tbody>
</table>

Summary

- RA is a chronic and costly disease from a payer perspective
- Drug treatment of RA is a major driver of specialty pharmacy cost
- Treatment approaches are changing and guidelines are moving towards earlier and more aggressive treatment
- Yet, current treatment often is sub optimal
- Payers are challenged to get the most value from RA treatments
- Management of the space will get more complex in the near future
Questions