Targeted Immune Modulators for Rheumatoid Arthritis: Effectiveness & Value

Public Meeting – March 24, 2017
Welcome and Introduction

• New England Comparative Effectiveness Public Advisory Council (CEPAC)

• The Institute for Clinical and Economic Review (ICER)
Sources of Funding, 2017

- Non-profit foundations: 78%
- Manufacturer grants, contracts and contributions: 10%
- Contributions from health plans and provider groups: 9%
- ICER Policy Summit only: 3%
Welcome and Introduction

• Why are we here today?
  • Innovation bringing substantial benefits to patients, their families, communities, and society

  • “When our arthritis community began in 1999 our patient events were held in wheelchair-accessible locations with ample space for up to one-third of the participants and their wheelchairs or other assistive devices. Patients were overwhelmingly on cDMARD therapy such as Methotrexate. Biologics, not Methotrexate, took away the wheelchairs.”

  -- Global Healthy Living public comments
Welcome and Introduction

• Why are we here today?
  • Difficulties accessing drugs
    • Step therapy protocols
    • Requirements to switch drugs with new insurance
    • High out-of-pocket costs for patients

• Cost to the system, prices, and value
## Drug net price inflation and value

<table>
<thead>
<tr>
<th>Drug</th>
<th>Net price 2016</th>
<th>Price to meet $150K/QALY</th>
<th>Year at that price or lower</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rituximab</td>
<td>$710</td>
<td>$534</td>
<td>2009</td>
</tr>
<tr>
<td>Abatacept sc</td>
<td>$814</td>
<td>$540</td>
<td>2013</td>
</tr>
<tr>
<td>Tocilizumab sc</td>
<td>$719</td>
<td>$614</td>
<td>2015</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>$1,554</td>
<td>$978</td>
<td>2013</td>
</tr>
<tr>
<td>Certolizumab peg</td>
<td>$1,288</td>
<td>$875</td>
<td>2013</td>
</tr>
<tr>
<td>Etanercept</td>
<td>$777</td>
<td>$504</td>
<td>2014</td>
</tr>
<tr>
<td>Golimumab sc</td>
<td>$2,905</td>
<td>$1,593</td>
<td>2012</td>
</tr>
<tr>
<td>Infliximab</td>
<td>$817</td>
<td>$598</td>
<td>2010</td>
</tr>
</tbody>
</table>
Welcome and Introduction

How was the ICER report on treatments for RA developed?

- Scoping with guidance from patient groups, clinical experts, manufacturers, and other stakeholders
- Internal ICER staff evidence analysis
- University of Washington cost-effectiveness modeling
- Public comment and revision
- Clinical expert report reviewers
  - Andrew Concoff, MD
  - Max Hamburger, MD
  - Andrew Laster, MD
  - Kent Johnson, MD
  - Matthew Liang, MD, MPH
  - Elizabeth Tindall, MD
- Patient expert report reviewers
  - Arthritis Foundation: Sandie Preiss, MPA; Guy Eakin, PhD; and Kayla Amodeo, PhD
  - Janet Stearns Wyatt, PhD, RN, FAANP
- How is the evidence report structured to support CEPAC voting and policy discussion?
Goal: Sustainable Access to High-Value Care for All Patients

Long-Term Value for Money
- Comparative Clinical Effectiveness
- Other Benefits or Disadvantages
- Estimated Incremental cost-effectiveness
- Contextual Considerations

Short-Term Affordability
- Potential Budget Impact
Agenda

9:30am: Welcome and Opening Remarks
9:45am: The Patient Experience: Accessing Care
   The Arthritis Foundation
9:55am. Presentation of the Evidence
   Evidence Review: Daniel A. Ollendorf, PhD, ICER
   Comparative Value: Jonathan Campbell, PhD, University of Colorado School of Pharmacy
10:50am: Manufacturer Public Comments: Panel & Discussion
11:40pm: Public Comments and Discussion
12:15pm: Lunch
1:00pm: New England CEPAC Deliberation and Votes
2:00pm: Policy Roundtable
3:30pm: Reflections and Wrap Up
4:00pm: Meeting Adjourned
Surveys

The AF conducted 3 patient surveys to help inform ICER of the patient experience

1. Rheumatoid Arthritis: Patient Treatment Experiences
2. Impact of Innovative Therapies on Rheumatoid Arthritis Patients
3. Utilization Management Survey

Limitations:

• Self reported data
• Not generalizable to other chronic diseases
• Cross-sectional design
Rheumatoid Arthritis: Patient Treatment Experiences

Survey 1
Methodology

- Delivery method: Online survey; Qualtrics software
- Population: Arthritis Foundation constituents with expressed interest in RA
- Dates open: November 3-16, 2016
- Total Responses: $n = 3,186$
People with RA often had to change medications early in their course of treatment

<table>
<thead>
<tr>
<th>Medication</th>
<th>1-2 years</th>
<th>3-4 years</th>
<th>5+ years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Xeljanz® (tofacitinib)</td>
<td>93%</td>
<td>7%</td>
<td>0%</td>
</tr>
<tr>
<td>Actemra® (tocilizumab)</td>
<td>82%</td>
<td>10%</td>
<td>8%</td>
</tr>
<tr>
<td>Ocrevus® (abatacept)</td>
<td>77%</td>
<td>15%</td>
<td>9%</td>
</tr>
<tr>
<td>Rituxan® (rituximab)</td>
<td>77%</td>
<td>12%</td>
<td>10%</td>
</tr>
<tr>
<td>Remicade® (infliximab)</td>
<td>52%</td>
<td>16%</td>
<td>32%</td>
</tr>
<tr>
<td>Simponi® (golimumab)</td>
<td>88%</td>
<td>3%</td>
<td>1%</td>
</tr>
<tr>
<td>Cimzia® (certolizumab pegol)</td>
<td>91%</td>
<td>11%</td>
<td>8%</td>
</tr>
<tr>
<td>Enbrel® (etanercept)</td>
<td>56%</td>
<td>13%</td>
<td>30%</td>
</tr>
<tr>
<td>Humira® (adalimumab)</td>
<td>84%</td>
<td>7%</td>
<td>9%</td>
</tr>
<tr>
<td>Other (please specify)</td>
<td>50%</td>
<td>14%</td>
<td>36%</td>
</tr>
</tbody>
</table>

Q - If applicable, how many MONTHS have you been on (or were you on) each medication? Mark all that apply. n=1,769

Top “other” answers:
- Methotrexate
- Plaquenil
- Prednisone
Most respondents have taken multiple medications over the course of their RA treatment

<table>
<thead>
<tr>
<th>Drug</th>
<th>First Medication</th>
<th>Second Medication</th>
<th>Third Medication</th>
<th>Fourth Medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Xeljanz® (tofacitinib)</td>
<td>13%</td>
<td>15%</td>
<td>34%</td>
<td>47%</td>
</tr>
<tr>
<td>Actemra® (tocilizumab)</td>
<td>1%</td>
<td>23%</td>
<td>32%</td>
<td>44%</td>
</tr>
<tr>
<td>Ocrevus® (abatacept)</td>
<td>26%</td>
<td>26%</td>
<td>38%</td>
<td>29%</td>
</tr>
<tr>
<td>Rituxan® (rituximab)</td>
<td>23%</td>
<td>23%</td>
<td>36%</td>
<td>34%</td>
</tr>
<tr>
<td>Remicade® (infliximab)</td>
<td>37%</td>
<td>31%</td>
<td>19%</td>
<td>13%</td>
</tr>
<tr>
<td>Simponi® (golimumab)</td>
<td>35%</td>
<td>28%</td>
<td>32%</td>
<td>32%</td>
</tr>
<tr>
<td>Cimzia® (certolizumab pegol)</td>
<td>11%</td>
<td>25%</td>
<td>32%</td>
<td>32%</td>
</tr>
<tr>
<td>Enbrel® (etanercept)</td>
<td>45%</td>
<td>34%</td>
<td>11%</td>
<td>10%</td>
</tr>
<tr>
<td>Humira® (adalimumab)</td>
<td>33%</td>
<td>39%</td>
<td>22%</td>
<td>8%</td>
</tr>
<tr>
<td>Other (please specify)</td>
<td>28%</td>
<td>12%</td>
<td>5%</td>
<td>3%</td>
</tr>
</tbody>
</table>

Top “other” answers:
- Methotrexate
- Plaquinil
- Prednisone

Q - If you have taken multiple drugs for RA overtime, please indicate which drugs you took first, second, etc. n=596
Utilization Management: Step Therapy

“HAVE YOU EVER BEEN TOLD THAT YOU HAD TO GO THROUGH A STEP THERAPY PROCESS FOR YOUR PRESCRIPTION MEDICATION NEEDS?”

- **YES**: 45%
- **NO**: 47%
- **Not Sure**: 8%
Impact of Innovative Therapies on Rheumatoid Arthritis Patients

Survey 2
Methodology

• Delivery method: Online survey; Qualtrics software

• Population: Arthritis Foundation constituents with rheumatoid arthritis

• Dates open: November 29 – December 1, 2016

• Total responses: $n=559$
  • Biologic Naïve: $n=222$
    • Biologic naïve for 5 years or more
    • Biologic experienced $n=337$
      • Biologic experienced within 5 years
Biologic naïve patients were **38% more likely** to have experienced joint damage because of their arthritis.

**Q. Have you experienced joint damage because of your arthritis?**

- **Yes**: 90% Biologic Naïve, 65% Biologic Experienced
- **No**: 3% Biologic Naïve, 11% Biologic Experienced
- **Not Sure**: 7% Biologic Naïve, 24% Biologic Experienced

*Biologic naïve for at least 5 years (n=222); Biologic experienced within 5 years (n=337)*
Biologic naïve patients were **over 400% more likely** to have **7 or more** joint replacements or other major surgeries such as a fusion.

- **7 or more**: Biologic Naïve 33%, Biologic Experienced 6%
- **5-6**: Biologic Naïve 17%, Biologic Experienced 8%
- **3-4**: Biologic Naïve 20%, Biologic Experienced 21%
- **1-2**: Biologic Naïve 31%, Biologic Experienced 65%

Q. How many joint surgeries or fusions have you had?

- Biologic naïve for at least 5 years (n=222)
- Biologic experienced within 5 years (n=337)
Biologic naïve patients are **44% more likely** to report going on disability

- **Yes**: Biologic Naïve (41%) vs. Biologic Experienced (28%)
- **No**: Biologic Naïve (56%) vs. Biologic Experienced (70%)
- **Not sure**: Biologic Naïve (3%) vs. Biologic Experienced (2%)

Q. Have you EVER had to go on disability?
Biologic naïve patients were **66% more likely** to be hospitalized or visit the ER when their disease was not well controlled by medication.

- **I missed work/school**: 62% Biologic Naïve, 58% Biologic Experienced
- **I required physical or occupational therapy**: 61% Biologic Naïve, 44% Biologic Experienced
- **I developed new or worse damage in joints**: 59% Biologic Naïve, 35% Biologic Experienced
- **I lost or had to leave my job/school**: 38% Biologic Naïve, 32% Biologic Experienced
- **I was hospitalized or had to go to the ER**: 31% Biologic Naïve, 18% Biologic Experienced

Q. Have you EVER experienced the following impacts when your disease was not well controlled while on medication? Please check all that apply.
Biologic naïve patients were more likely to indicate they have a “problem/major problem” with the following:

- Going up and down stairs: 41% (Naïve) vs 37% (Experienced)
- Walking for more than 10 minutes: 31% (Naïve) vs 28% (Experienced)
- Dressing myself, including tying shoelaces and doing buttons: 21% (Naïve) vs 10% (Experienced)
- Preparing meals: 18% (Naïve) vs 15% (Experienced)
- Using cutlery to eat food: 12% (Naïve) vs 10% (Experienced)

Q. To what extent is each of the following a problem for you as a result of your RA?
Summary

• RA is a complex disease requiring personalized, nuanced care
• Patients have to cycle through many treatments before becoming stable
• Patients need continued access to all treatments available
QUESTIONS?
Key Review Team Members

Foluso Agboola, MBBS, MPH
Shanshan Liu, MS, MPH
Patty Synnott, MALD, MS

We have no conflicts to disclose.
Topic in Context
Background: Rheumatoid Arthritis (RA)

• Most common chronic inflammatory arthritis in adults
• 1.3-1.8 million Americans affected
  – Occurs at any age; peak incidence at 50-60 years
  – More common in women
• Two key types of medication
  – Conventional DMARDs (e.g., methotrexate)
  – Targeted immune modulators (TIMs)
• Disease course
  – Progressive disability and shortened lifespan historically
  – Improvements in survival and other outcomes seen in era of earlier diagnosis and aggressive use of TIMs
RA in Context

• Complex disease to diagnose and manage
  – Multiple phenotypic and genotypic variations in pathogenesis of RA and response to treatment

• Evolution of management:
  – Aggressive treatment in patients with poor prognostic factors
  – Close surveillance of disease activity, frequent adjustments to treatment
  – Goal: Clinical remission or low levels of disease activity
Input from Patients and Patient Groups

- Insurance requirements/limits on therapy sequencing/switching burdensome

- Self-injection may limit valuable provider interaction vs. clinic-based infusion

- Financial challenges include drug costs and care coordination, lost work/school time, etc.

- Additional patient-centric measures required on symptom control, side effects, ADLs, etc.

- RA is heterogeneous and labile – “point in time” measures do not capture this well
RA in Context: Ongoing Challenges

• Shortage of available rheumatologists
• Time to diagnosis issues
• Rising list prices for TIMs in recent years
  – Adalimumab and Etanercept: ↑ 70-80% in last three years (now currently ~$4,000/month)
  – Potential out-of-pocket exposure for Medicare patients: $1,600 - $4,500 annually
# TIMs for RA

<table>
<thead>
<tr>
<th>Class</th>
<th>Drug</th>
<th>Brand name</th>
<th>Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>TNF Inhibitors</td>
<td>Adalimumab</td>
<td>Humira</td>
<td>SC</td>
</tr>
<tr>
<td></td>
<td>Certolizumab Pegol</td>
<td>Cimzia</td>
<td>SC</td>
</tr>
<tr>
<td></td>
<td>Etanercept</td>
<td>Enbrel</td>
<td>SC</td>
</tr>
<tr>
<td></td>
<td>Golimumab</td>
<td>Simponi, Simponi Aria</td>
<td>SC or IV</td>
</tr>
<tr>
<td>IL-6 inhibitor</td>
<td>Sarilumab</td>
<td>Kevzara</td>
<td>SC</td>
</tr>
<tr>
<td></td>
<td>Tocilizumab</td>
<td>Actemra</td>
<td>SC or IV</td>
</tr>
<tr>
<td>JAK inhibitors</td>
<td>Baricitinib</td>
<td>Olumiant</td>
<td>PO</td>
</tr>
<tr>
<td></td>
<td>Tofacitinib</td>
<td>Xeljanz</td>
<td>PO</td>
</tr>
<tr>
<td>IL-6 inhibitor</td>
<td>Tocilizumab</td>
<td>Actemra</td>
<td>SC or IV</td>
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<td>JAK inhibitors</td>
<td>Baricitinib</td>
<td>Olumiant</td>
<td>PO</td>
</tr>
<tr>
<td></td>
<td>Tofacitinib</td>
<td>Xeljanz</td>
<td>PO</td>
</tr>
</tbody>
</table>
Evidence Review
Overview

• **Target population**: moderately-to-severely active RA who experienced inadequate response to previous methotrexate or other conventional DMARD therapy

• **Interventions**: Combination therapy (TIM + conventional DMARD) or TIM monotherapy with 11 TIMs

• **Comparisons of interest**:
  - Head-to-head studies between TIMs
  - Conventional DMARD therapy alone
Key Outcomes

• Disease activity and remission (DAS28, CDAI, SDAI)
• Treatment response (ACR20, ACR50, and ACR70)
• Radiographic progression (modified total Sharp score)
• Function (HAQ-DI)
• Patient-reported outcomes (pain, fatigue, HrQoL)
• Productivity loss and healthcare utilization
• Harms
The Evidence

• 67 RCTs (8 head-to-head between TIMs), 17 observational studies
• Most of good quality
• Strong internal validity but early rescue and crossover from cDMARD arms (12-24 weeks) limits longer-term conclusions
• Challenges posed by use of different variants of certain measures (e.g., disease activity, radiographic progression) and their evolution over time
TIMs vs. Conventional DMARDs

• Studied most frequently in TIM-naïve or mixed (≥80% naïve) populations

• All TIMs generated statistically- and clinically-significant improvements over cDMARDs alone:
  – NNTs to achieve clinical remission of 20 or less for all TIMs
  – ≥90% increase in proportion of patients achieving ACR20 or better response (52-71% vs. 27%)

• Benefits seen for both combination and monotherapy approaches
Head-to-Head Studies of TIMs: Overview

• 8 head to head RCTs involving 9 TIMs
• Adalimumab the comparator in all but one trial
• 4 trials involved the newer IL-6 and JAK inhibitors
## Head-to-Head RCTs of TIMs vs. Adalimumab: Combination Therapy

<table>
<thead>
<tr>
<th>Drug</th>
<th>n</th>
<th>Low Disease Activity/Remission</th>
<th>ACR Response</th>
<th>Radiographic Progression</th>
<th>HAQ-DI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abatacept (SC)</td>
<td>646</td>
<td>⇔</td>
<td>⇔</td>
<td>⇔</td>
<td>⇔</td>
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<tr>
<td>Tofacitinib</td>
<td>717</td>
<td>⇔</td>
<td>⇔</td>
<td>ND</td>
<td>⇔</td>
</tr>
<tr>
<td>Baricitinib</td>
<td>1307</td>
<td>↑</td>
<td>↑</td>
<td>⇔</td>
<td>↑</td>
</tr>
<tr>
<td>Certolizumab Pegol</td>
<td>915</td>
<td>⇔</td>
<td>⇔</td>
<td>ND</td>
<td>⇔</td>
</tr>
<tr>
<td>Etanercept</td>
<td>125</td>
<td>⇔</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
</tbody>
</table>

### Legend
- Superior: ↑
- Comparable: ⇔
- Inferior: ↓
- No Data Identified: ND
# Head-to-Head RCTs of TIMs vs Adalimumab: Monotherapy

<table>
<thead>
<tr>
<th>TIM</th>
<th>n</th>
<th>Low Disease Activity/Remission</th>
<th>ACR Response</th>
<th>Radiographic Progression</th>
<th>HAQ-DI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sarilumab</td>
<td>369</td>
<td><img src="up" alt="up" /></td>
<td><img src="up" alt="up" /></td>
<td>ND</td>
<td><img src="up" alt="up" /></td>
</tr>
<tr>
<td>Tocilizumab</td>
<td>326</td>
<td><img src="up" alt="up" /></td>
<td><img src="up" alt="up" /></td>
<td>ND</td>
<td><img src="leftrightarrow" alt="leftrightarrow" /></td>
</tr>
</tbody>
</table>

- **Superior**: ![up](up)
- **Comparable**: ![leftrightarrow](leftrightarrow)
- **Inferior**: ![down](down)
- **No Data Identified**: ND
Network Meta-Analysis: Combination Therapy

DMARD

ABT (iv) + DMARD

SAR + DMARD

TOF + DMARD

ADA + DMARD

IFX + DMARD

ABT (sc) + DMARD

BAR + DMARD

ETN + DMARD

CTZ + DMARD

GOL (iv) + DMARD

TCZ (sc) + DMARD

TCZ (iv) + DMARD

GOL (sc) + DMARD

RTX + DMARD

Int DMARD

TCZ (sc)

ABT (sc)

IFX

CTZ
Network Meta-Analysis: Monotherapy

[Diagram showing relationships between ADA, SAR, TCZ (iv), DMARD, and ETN with numbers indicating the strength of the relationship.]
Network Meta-Analyses

• No statistical differences between TIMs when used in combination with cDMARDs
• Greater likelihood of ACR response with tocilizumab and sarilumab monotherapy vs. adalimumab
  – Echoes results of head-to-head studies
• Findings consistent with other published SRs and NMAs
Harms

• Frequently reported adverse events: mild infections, injection site reactions, and infusion reactions

• Overall incidence of serious AEs, serious infections, malignancies, and deaths comparable between TIMs
  – Serious infection in longer-term trials somewhat higher with infliximab (9 per 100 P-Y vs. 2-3 for other TIMs)

• Long-term observational data primarily for TNFα inhibitors:
  – No consistent or material differences in available studies
Black Box Warnings

• All FDA-approved TIMs (except abatacept) have black box warnings

• Tocilizumab
  • Serious infection

• Tofacitinib
  • Serious infection, lymphoma/malignancy, lymphoproliferative disorder in renal transplant patients

• TNFα-inhibitors,
  • Serious infection, lymphoma/malignancy (primarily children & adolescents)

• Rituximab
  • Fatal infusion reactions, severe mucocutaneous reactions, Hepatitis B reactivation, PML
Controversies & Uncertainties

- Head-to-head data from only 8 of 67 RCTs
- Patients do not feel that current PRO tools sufficiently capture their experience
- Need to identify predictors of treatment response
- Early crossover in DMARD-controlled trials may limit conclusions w/r/t longer-term outcomes
- Limited and emerging data on the effects of treatment sequencing, dose tapering, etc.
- Long-term effects of prolonged immunomodulation not well-understood for all TIMs
<table>
<thead>
<tr>
<th>Intervention</th>
<th>Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Monotherapy</strong></td>
<td></td>
</tr>
<tr>
<td>Sarilumab</td>
<td>B+</td>
</tr>
<tr>
<td>Tocilizumab</td>
<td>B+</td>
</tr>
<tr>
<td><strong>Combination Therapy</strong></td>
<td></td>
</tr>
<tr>
<td>Baricitinib</td>
<td>C+</td>
</tr>
<tr>
<td>Tofacitinib</td>
<td>C</td>
</tr>
<tr>
<td>Abatacept (sc)</td>
<td>C</td>
</tr>
<tr>
<td>Certolizumab pegol</td>
<td>C</td>
</tr>
<tr>
<td>Etanercept</td>
<td>C</td>
</tr>
</tbody>
</table>
Other Benefits or Disadvantages

• Rapid return to function and work for certain patients and their caregivers

• Downstream clinical benefits (e.g., reduced need for disability aids, joint replacement)

• Availability of 5 distinct classes of TIMs critical, given frequent switch patterns observed

• Routes of administration
  • Baricitinib and Tofacitinib are oral agents, may be preferable for those with concerns about self-injection or infusion
Summary

• Evidence base accumulated over ~20 years documents substantial benefits of TIM therapy over conventional DMARDs alone

• IL-6 and JAK inhibitors comparable or superior to adalimumab in head-to-head studies
  – Greater uncertainly on long-term safety

• Outside of head-to-head trials vs. adalimumab, evidence not adequate to distinguish TIM effectiveness or safety
Public Comments Received

- Over-reliance on RCT data to inform evidence base, despite availability of RWE
- Step therapy requirements not just economically-driven; may reflect certainty in long-term safety, for example
- Differences in trial populations biases NMA
- Some trials originally described as head-to-head were not
- ICER report draws conclusions primarily based on ACR response
Long-term Cost-Effectiveness

Jonathan D. Campbell, PhD
Department of Clinical Pharmacy
Center for Pharmaceutical Outcomes Research
University of Colorado Anschutz Medical Campus
Acknowledgements and Disclosures

• Collaborators:
  • Melanie Whittington, University of Colorado
  • R. Brett McQueen, University of Colorado
  • Varun Kumar, ICER
  • Rick Chapman, ICER
  • Dan Ollendorf, ICER

• The University of Colorado researchers report no industry funding related to rheumatoid arthritis.
Objective

To model the costs and outcomes for 11 targeted immune modulators (TIMs) relative to conventional disease-modifying anti-rheumatic drugs (cDMARDs) for adults with moderately-to-severely active rheumatoid arthritis.
Methods in Brief
Methods Overview (1)

- Population: Adults (average age 55 years) with moderately-to-severely active rheumatoid arthritis and inadequate response to or intolerance to prior therapy
- Setting: United States
- Perspective: Payer (direct medical care and drug costs)
- Comparators: Conventional DMARDs alone; and adalimumab (market leader)
- Time Horizon: Lifetime
- Discount Rate: 3% per year (costs and outcomes)
Methods Overview (2)

• Model: Sequential treatment cohort model (Markov cohort model)

• Cycle Length: 6 months

• Primary Outcome: Cost per quality-adjusted life year (QALY) gained
  • QALYs derived from Healthcare Assessment Questionnaire (HAQ) for Rheumatoid Arthritis score
  • HAQ score is a function of American College of Rheumatology (ACR) improvement criteria and modified Total Sharp Score (mTSS)
Use of a TIM in adult patients with moderately-to-severely active RA who have an inadequate response to prior therapy

**Model Schematic**

Initiate first drug in sequence → Treatment response at 6 months → Adjust efficacy for previous failure → Initiate next treatment in sequence

**Responders** ACR≥20

Function of ACR categories and mean difference in Total Sharp Score

**HAQ Score**

Function of HAQ and probability of hospitalization

Function of employment status, absenteeism, and HAQ

Function of mortality rate and HAQ

Function of age, disease duration, baseline HAQ, gender, previous number of DMARDs, and current HAQ

**Hospitalizations**

**Productivity Losses**

**Mortality Rate**

**Utility**

**Costs**

**QALYs**

* Productivity losses are only included in a societal perspective (not payer perspective)
Key Model Assumptions

• Longer time on conventional DMARD therapy alone was associated with larger HAQ degradations (linear assumption).

• Longer time on a TIM was associated with larger mTSS benefits (linear assumption).

• Patients could discontinue treatment for two reasons:
  1. Lack of effectiveness,
  2. Occurrence of an adverse event.

• Efficacy of subsequent TIM treatments is assumed to be reduced (Hazard ratio: 0.84).
Model Sequential Treatment Pattern

Treatment 1: First TIM
- *TNF-inhibitors*
  - adalimumab
  - certolizumab pegol
  - etanercept
  - golimumab
  - infliximab
- *Non-TNF-inhibitors*
  - rituximab
  - abatacept
  - tocilizumab
  - sarilumab
- *JAK-inhibitors*
  - tofacitinib
  - baricitinib

Treatment 2: Different TIM within same treatment category
- All other TNF-inhibitors
- All other non-TNF-inhibitors
- Other JAK-inhibitor

Treatment 3: Different TIM within different treatment categories
- Market basket of all TIMS excluding TNF-inhibitors
- Market basket of all TIMS excluding non-TNF-inhibitors
- Market basket of all TIMS excluding JAK-inhibitors

Treatment 4: Palliative care
- Conventional DMARD therapy
Parameters: Discontinuation and Serious Adverse Events

- TIM discontinuation due to adverse events ranged from 3.5% to 7.4% per year (review of clinical trial literature).
- Serious adverse events were modeled by TIM, based on a review of the literature.
  - A serious infection case was assigned a disutility of -0.16 for one month and $13,747 (assumed 2/3 pneumonia; 1/3 cellulitis).
  - A tuberculosis case was assigned a disutility of -0.16 for two months and a cost of $12,220.
<table>
<thead>
<tr>
<th>Intervention</th>
<th>Route</th>
<th>Discounted WAC*</th>
<th>Annual Drug Cost*</th>
</tr>
</thead>
<tbody>
<tr>
<td>rituximab</td>
<td>IV</td>
<td>$710</td>
<td>$30,764</td>
</tr>
<tr>
<td>abatacept</td>
<td>IV</td>
<td>$691</td>
<td>$27,637</td>
</tr>
<tr>
<td>abatacept</td>
<td>SC</td>
<td>$814</td>
<td>$42,306</td>
</tr>
<tr>
<td>tocilizumab</td>
<td>IV</td>
<td>$76</td>
<td>$27,627</td>
</tr>
<tr>
<td>tocilizumab</td>
<td>SC</td>
<td>$719</td>
<td>$21,861</td>
</tr>
<tr>
<td>sarilumab**</td>
<td>SC</td>
<td>----------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>tofacitinib</td>
<td>ORAL</td>
<td>$60</td>
<td>$43,873</td>
</tr>
<tr>
<td>baricitinib**</td>
<td>ORAL</td>
<td>----------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>adalimumab</td>
<td>SC</td>
<td>$1,554</td>
<td>$40,415</td>
</tr>
<tr>
<td>certolizumab pegol</td>
<td>SC</td>
<td>$1,288</td>
<td>$34,775</td>
</tr>
<tr>
<td>etanercept</td>
<td>SC</td>
<td>$777</td>
<td>$40,422</td>
</tr>
<tr>
<td>golimumab</td>
<td>SC</td>
<td>$2,905</td>
<td>$34,863</td>
</tr>
<tr>
<td>golimumab</td>
<td>IV</td>
<td>$1,114</td>
<td>$29,719</td>
</tr>
<tr>
<td>infliximab</td>
<td>IV</td>
<td>$817</td>
<td>$28,906</td>
</tr>
<tr>
<td>cDMARD (methotrexate)</td>
<td>ORAL</td>
<td>Generic</td>
<td>$1,155</td>
</tr>
</tbody>
</table>

*WAC as of February 2017, discounted to match SSR Health discounts by class;

**For investigational drugs, no annual cost was assumed, except the cost needed to achieve thresholds;

†Annual drug cost only includes cost of drug therapy, and not any costs associated with administration or monitoring. Annual drug costs reported in this table were average over three years of treatment, assuming 100% compliance to reduce variation of loading dosing schedule.
Model Results
# Base-Case for TIMs + Conventional DMARDs

<table>
<thead>
<tr>
<th>Treatment 1</th>
<th>Drug Cost</th>
<th>Total Payer Cost</th>
<th>Average HAQ</th>
<th>Life Years</th>
<th>QALYs</th>
</tr>
</thead>
<tbody>
<tr>
<td>rituximab</td>
<td>$366,768</td>
<td>$464,864</td>
<td>1.25</td>
<td>16.79</td>
<td>12.70</td>
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<tr>
<td>abatacept (iv)</td>
<td>$367,724</td>
<td>$466,733</td>
<td>1.22</td>
<td>16.82</td>
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<tr>
<td>abatacept (sc)</td>
<td>$452,292</td>
<td>$566,053</td>
<td>1.18</td>
<td>16.87</td>
<td>12.90</td>
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<td>tocilizumab (iv)</td>
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<td>12.88</td>
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<td>tocilizumab (sc)</td>
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<td>16.83</td>
<td>12.81</td>
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<tr>
<td>sarilumab</td>
<td>-</td>
<td>-</td>
<td>1.21</td>
<td>16.83</td>
<td>12.81</td>
</tr>
<tr>
<td>tofacitinib</td>
<td>$467,784</td>
<td>$579,140</td>
<td>1.28</td>
<td>16.75</td>
<td>12.57</td>
</tr>
<tr>
<td>baricitinib</td>
<td>-</td>
<td>-</td>
<td>1.25</td>
<td>16.78</td>
<td>12.67</td>
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<tr>
<td>adalimumab</td>
<td>$425,929</td>
<td>$530,720</td>
<td>1.25</td>
<td>16.78</td>
<td>12.68</td>
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<tr>
<td>certolizumab pegol</td>
<td>$417,742</td>
<td>$522,473</td>
<td>1.20</td>
<td>16.84</td>
<td>12.86</td>
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<tr>
<td>etanercept</td>
<td>$470,007</td>
<td>$583,449</td>
<td>1.12</td>
<td>16.94</td>
<td>13.12</td>
</tr>
<tr>
<td>golimumab (sc)</td>
<td>$408,413</td>
<td>$512,875</td>
<td>1.25</td>
<td>16.79</td>
<td>12.69</td>
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<tr>
<td>golimumab (iv)</td>
<td>$386,971</td>
<td>$488,380</td>
<td>1.23</td>
<td>16.81</td>
<td>12.75</td>
</tr>
<tr>
<td>infliximab</td>
<td>$381,243</td>
<td>$480,448</td>
<td>1.24</td>
<td>16.79</td>
<td>12.73</td>
</tr>
<tr>
<td>cDMARD</td>
<td>$18,209</td>
<td>$67,819</td>
<td>1.78</td>
<td>16.16</td>
<td>10.69</td>
</tr>
</tbody>
</table>
# Results for TIMs as Monotherapy

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Drug Cost</th>
<th>Total Payer Cost</th>
<th>Average HAQ</th>
<th>Life Years</th>
<th>QALYs</th>
</tr>
</thead>
<tbody>
<tr>
<td>tocilizumab (iv)</td>
<td>$384,441</td>
<td>$489,541</td>
<td>1.05</td>
<td>17.03</td>
<td>13.35</td>
</tr>
<tr>
<td>sarilumab</td>
<td>-</td>
<td>-</td>
<td>1.07</td>
<td>17.00</td>
<td>13.28</td>
</tr>
<tr>
<td>adalimumab</td>
<td>$449,224</td>
<td>$562,748</td>
<td>1.17</td>
<td>16.89</td>
<td>12.95</td>
</tr>
<tr>
<td>etanercept</td>
<td>$469,981</td>
<td>$584,952</td>
<td>1.11</td>
<td>16.95</td>
<td>13.16</td>
</tr>
<tr>
<td>cDMARD</td>
<td>$18,235</td>
<td>$67,525</td>
<td>1.76</td>
<td>16.18</td>
<td>10.75</td>
</tr>
</tbody>
</table>
## Incremental Cost-Effectiveness Ratios for the Base Case, TIMs + conventional DMARD

<table>
<thead>
<tr>
<th>Treatment 1</th>
<th>ICER (cost per QALY gained) Comparator: cDMARD</th>
<th>ICER (cost per QALY gained) Comparator: adalimumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>rituximab</td>
<td>$198,056</td>
<td>Less costly, More effective</td>
</tr>
<tr>
<td>abatacept (iv)</td>
<td>$191,317</td>
<td>Less costly, More effective</td>
</tr>
<tr>
<td>abatacept (sc)</td>
<td>$225,853</td>
<td>$163,376</td>
</tr>
<tr>
<td>tocilizumab (iv)</td>
<td>$183,949</td>
<td>Less costly, More effective</td>
</tr>
<tr>
<td>tocilizumab (sc)</td>
<td>$168,660</td>
<td>Less costly, More effective</td>
</tr>
<tr>
<td>tofacitinib</td>
<td>$271,749</td>
<td>More costly, Less effective</td>
</tr>
<tr>
<td>adalimumab</td>
<td>$232,644</td>
<td>Reference</td>
</tr>
<tr>
<td>certolizumab pegol</td>
<td>$209,736</td>
<td>Less costly, More effective</td>
</tr>
<tr>
<td>etanercept</td>
<td>$212,021</td>
<td>$119,233</td>
</tr>
<tr>
<td>golimumab (sc)</td>
<td>$222,380</td>
<td>Less costly, More effective</td>
</tr>
<tr>
<td>golimumab (iv)</td>
<td>$204,212</td>
<td>Less costly, More effective</td>
</tr>
<tr>
<td>infliximab</td>
<td>$202,824</td>
<td>Less costly, More effective</td>
</tr>
</tbody>
</table>
## Incremental Cost-Effectiveness Ratios for TIMs as Monotherapy

<table>
<thead>
<tr>
<th>Treatment 1</th>
<th>ICER (cost per QALY gained) Comparator: cDMARD</th>
<th>ICER (cost per QALY gained) Comparator: adalimumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>tocilizumab (iv)</td>
<td>$162,038</td>
<td>Less costly, More effective</td>
</tr>
<tr>
<td>adalimumab</td>
<td>$225,423</td>
<td>Reference case</td>
</tr>
<tr>
<td>etanercept</td>
<td>$214,427</td>
<td>$102,697</td>
</tr>
</tbody>
</table>
Tornado Diagram for Tocilizumab
Subcutaneous versus Conventional DMARD

HAQ degradation (annual) for cDMARD
tocilizumab (sc) Adverse Event Discontinuation Rate (per person half year)
Baseline HAQ
Coefficient on TSS for HAQ
HAQ >70 Drop
HAQ 50-70 Drop
tocilizumab (sc) TSS mean difference
HAQ 20-50 Drop
HAQ <20 Drop
Cost per hospital day
Hospital days per HAQ
HAQ correction for time on trt related to tss change
Efficacy of secondary DMARDs after failure
Cost of intravenous treatment administration (first hour)
Baseline TSS

$130,000 $150,000 $170,000 $190,000 $210,000 $230,000
Probabilistic Sensitivity Analysis (PSA) Results: TIMs vs. conventional DMARD therapy

<table>
<thead>
<tr>
<th>Drug</th>
<th>Cost-Effective at $50,000 per QALY</th>
<th>Cost-Effective at $100,000 per QALY</th>
<th>Cost-Effective at $150,000 per QALY</th>
</tr>
</thead>
<tbody>
<tr>
<td>rituximab</td>
<td>0%</td>
<td>0%</td>
<td>4%</td>
</tr>
<tr>
<td>abatacept (iv)</td>
<td>0%</td>
<td>0%</td>
<td>4%</td>
</tr>
<tr>
<td>abatacept (sc)</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>tocilizumab (iv)</td>
<td>0%</td>
<td>0%</td>
<td>10%</td>
</tr>
<tr>
<td>tocilizumab (sc)</td>
<td>0%</td>
<td>0%</td>
<td>27%</td>
</tr>
<tr>
<td>tofacitinib</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>adalimumab</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>certolizumab pegol</td>
<td>0%</td>
<td>0%</td>
<td>1%</td>
</tr>
<tr>
<td>etanercept</td>
<td>0%</td>
<td>0%</td>
<td>1%</td>
</tr>
<tr>
<td>golimumab (sc)</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>golimumab (iv)</td>
<td>0%</td>
<td>0%</td>
<td>1%</td>
</tr>
<tr>
<td>infliximab</td>
<td>0%</td>
<td>0%</td>
<td>2%</td>
</tr>
</tbody>
</table>
PSA Results: Cost-Effectiveness Clouds
Tocilizumab (sc) vs. Adalimumab (Comb. w/MTX)
PSA Results: Cost-Effectiveness Clouds
Tofacitinib vs. Adalimumab (Comb. w/MTX)
Scenario Analysis Results

- Treatment 4 as Market Basket TIM resulted in slightly higher costs per QALY (vs. base-case).
- Societal perspective resulted in lower costs per QALY with tocilizumab (iv and sc) yielding costs per QALY in the $130,000 - $140,000/QALY range.
- Short-term time horizon findings were higher than base-case and were $75,000 - $125,000 per additional responder after year one.
- Experienced TIM population findings were slightly lower compared to base-case, but remained above $150,000/QALY.
Consequences of Treatment throughout Model Time Horizon
Limitations

• In clinical practice, treatment choice is often based on patients’ individual characteristics and risk factors, which may not be consistent with the model’s sequential treatment pattern.

• One universal hazard ratio for the reduced efficacy of subsequent treatments was assumed, due to the limited drug class-specific data available.
  – This reduced efficacy was tested in a one-way sensitivity analysis and suggested limited impact on the findings.

• Sequential patterns tended to move the cost-effectiveness findings closer to the average TIM with less possible separation across TIMs.
  – The sequential patterns within TIMs appears close to observations within registries of TIM discontinuation and switching.

• Uncertainty remains surrounding the long-term progressions of HAQ degradation for conventional DMARD and mTSS improvements for TIMs.
Summary

• Base-case findings suggest that all TIMs provide substantial clinical benefit in comparison to conventional DMARDs alone; their additional costs translate into cost-effectiveness estimates ranging from approximately $170,000 to $270,000 per QALY gained.

• Compared to the market leader adalimumab, most TIMs in combination with conventional DMARDs were more favorable.

• One-way sensitivity analyses suggested that annual HAQ degradation for conventional DMARDs was the most influential parameter.

• Probabilistic sensitivity analyses suggested that separation across TIMs appeared to be more in the cost domain rather than in the QALY domain.
Public Comments Summary

• Where possible, add more transparency and evidence of model validation

• Use best available evidence for forecasting the long-term costs and consequences of TIMs as well as conventional DMARDs

• Concerns over cohort model with limited patient-level heterogeneity

• TIM dosing was informed by trial evidence to connect the clinical signals with their corresponding cost
Public Comment: Manufacturer Representatives
# Public Comment: Manufacturer Representatives

<table>
<thead>
<tr>
<th>Name</th>
<th>Title</th>
<th>Company</th>
</tr>
</thead>
<tbody>
<tr>
<td>Margaret Michalska, MD</td>
<td>Associate Group Medical Director</td>
<td>Genentech</td>
</tr>
<tr>
<td>Brad Stolshek, Pharm.D.</td>
<td>Director, Global Health Economics – Inflammation</td>
<td>Amgen</td>
</tr>
<tr>
<td>Tammy Curtice, PharmD, MS</td>
<td>Director, Health Economics &amp; Outcomes Research</td>
<td>Bristol-Myers Squibb</td>
</tr>
<tr>
<td>Andrew Koenig D.O., F.A.C.R.</td>
<td>Inflammation &amp; Immunology Group Lead</td>
<td>Pfizer</td>
</tr>
<tr>
<td>Andreas Kuznik, Ph.D.</td>
<td>Senior Director</td>
<td>Regeneron Pharmaceuticals</td>
</tr>
<tr>
<td>Dr Jeff Stark</td>
<td>Head of Medical Affairs, Rheumatology</td>
<td>UCB</td>
</tr>
</tbody>
</table>
Public Comment
Dr. Christopher Phillips, American College of Rheumatology
Doctor

Conflicts of interest:

Receipt or potential receipt of anything of monetary value, including but not limited to, salary or other payments for services such as consulting fees or honoraria in excess of $5,000

Manufacturer support of research in the clinical area of this meeting in which you are participating

If yes, please describe the relationship(s) below.

Abbvie - speaker bureau
Abbvie - clinical research
Dr. Liana Fraenkel, Professor of Medicine, Yale

Conflicts of interest:

None to disclose
Chantelle Marcial, Global Healthy Living Foundation—Member

Conflicts of interest:

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Status or position as an officer, board member, trustee, owner or employee of a health care company, or an organization which receives more than 25% of its funding from health care companies

Manufacturer support of research in the clinical area of this meeting in which you are participating

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Janssen
Horizon Pharma
Genentech
Endo
Crescendo
Bristol Myers Squibb
AstraZeneca
Amgen
AbbVie
Arthritis Foundation

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Break for Lunch
Meeting will resume at 1:00PM
Voting Questions
1. Test Voting Question: The coldest day in Boston history was February 9th, 1934. What was the temperature on this day?

A. -22° F  
B. -6° F  
C. 0° F  
D. -18° F
Patient Population

*Patient population for all voting questions:* Patients age 18 and older with moderately-to-severely active rheumatoid arthritis and inadequate response to or intolerance of conventional DMARDs.
Comparative Effectiveness of Targeted Immune Modulators as Monotherapy
2. Is the evidence adequate to demonstrate that the net health benefit of tocilizumab monotherapy is superior to that provided by adalimumab monotherapy?

Yes  No
3. Is the evidence adequate to demonstrate that the net health benefit of sarilumab monotherapy is superior to that provided by adalimumab monotherapy?

Yes  No
4. Is the evidence adequate to distinguish the net health benefit between tocilizumab monotherapy and sarilumab monotherapy?

- Yes
- No
5. Is the evidence adequate to demonstrate that the net health benefit of tofacitinib monotherapy is superior to that provided by adalimumab monotherapy?

Yes  No
6. Is the evidence adequate to demonstrate that the net health benefit of baricitinib monotherapy is superior to that provided by adalimumab monotherapy?

Yes  No
7. Is the evidence adequate to distinguish the net health benefit between tofacitinib monotherapy and baricitinib monotherapy?

Yes  No
Comparative Effectiveness of Targeted Immune Modulators in Combination With cDMARDs
8. Is the evidence adequate to demonstrate that the net health benefit of tocilizumab + cDMARD therapy is superior to that provided by adalimumab + cDMARD therapy?

Yes  No
9. Is the evidence adequate to demonstrate that the net health benefit of sarilumab + cDMARD therapy is superior to that provided by adalimumab + cDMARD therapy?

Yes  No
10. Is the evidence adequate to distinguish the net health benefit between tocilizumab + cDMARD therapy and sarilumab + cDMARD therapy?

Yes  No
11. Is the evidence adequate to demonstrate that the net health benefit of tofacitinib + cDMARD therapy is superior to that provided by adalimumab + cDMARD therapy?

<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
</table>

12. Is the evidence adequate to demonstrate that the net health benefit of baricitinib + cDMARD therapy is superior to that provided by adalimumab + cDMARD therapy?

Yes

No
13. Is the evidence adequate to distinguish the net health benefit between tofacitinib + cDMARD therapy and baricitinib + cDMARD therapy?

Yes  No
Comparative Value of Targeted Immune Modulators (TIM)
14. Given the available evidence on comparative effectiveness and incremental cost-effectiveness, and considering other benefits, disadvantages, and contextual considerations, what is the long-term value for money for tocilizumab monotherapy in comparison to adalimumab monotherapy?

A. Low
B. Intermediate
C. High
15. Given the available evidence on comparative effectiveness and incremental cost-effectiveness, and considering other benefits, disadvantages, and contextual considerations, what is the long-term value for money for tocilizumab + cDMARD therapy in comparison to adalimumab + cDMARD therapy?

A. Low
B. Intermediate
C. High
Given the available evidence on comparative effectiveness and incremental cost-effectiveness, and considering other benefits, disadvantages, and contextual considerations, what is the long-term value for money for tofacitinib monotherapy in comparison to adalimumab monotherapy?

A. Low
B. Intermediate
C. High
17. Given the available evidence on comparative effectiveness and incremental cost-effectiveness, and considering other benefits, disadvantages, and contextual considerations, what is the long-term value for money for tofacitinib + cDMARD therapy in comparison to adalimumab + cDMARD therapy?

A. Low
B. Intermediate
C. High
Policy Roundtable
### Policy Roundtable

<table>
<thead>
<tr>
<th>Thomas Amoroso, MD, MPH</th>
<th>Himanshu R. Patel, D.O.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical Director for Medical Policy</td>
<td>Sr. Medical Advisor, Musculoskeletal Medicine</td>
</tr>
<tr>
<td>Tufts Health Plan</td>
<td>Eli Lilly and Company</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Andreas Kuznik, PhD</th>
<th>Sandie Preiss, MPA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Senior Director of HEOR</td>
<td>National Vice President</td>
</tr>
<tr>
<td>Regeneron Pharmaceuticals</td>
<td>Arthritis Foundation</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Andrew J. Laster, MD, FACR, CCD</th>
<th>Janet Stearns Wyatt, PhD, RN, FAANP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Board of Directors United Rheumatology</td>
<td>Patient, Volunteer for the Arthritis Foundation and</td>
</tr>
<tr>
<td>Arthritis &amp; Osteoporosis Consultants of the</td>
<td>Retired Nurse Practitioner</td>
</tr>
<tr>
<td>Carolinas</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Matthew H. Liang, MD, MPH</th>
<th>Robert Zavoski, MD, MPH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Professor of Medicine, Harvard Medical School</td>
<td>Medical Director</td>
</tr>
<tr>
<td>Division of Rheumatology, Immunology, and Allergy Brigham and Women's Hospital</td>
<td>Connecticut Department of Social Services</td>
</tr>
</tbody>
</table>
New England CEPAC Reflections
Adjourn
T-cell inhibitors-Abatacept

- There were two abatacept head to head RCTs
  - Abatacept (sc) versus adalimumab (both in combination with methotrexate)
  - Abatacept (iv) versus infliximab (both in combination with methotrexate)
- Abatacept was similar to adalimumab and infliximab in rates of remission, ACR response, and improvement in HAQ-DI and other patient reported outcomes at 24 weeks
- No statistical difference between abatacept and adalimumab in slowing radiographic progression at 1 year
IL-6-Inhibitors - Tocilizumab

• One head to head RCT was identified of tocilizumab monotherapy versus adalimumumab monotherapy

• Tocilizumab was superior to adalimumab in achieving:
  
  • Low disease activity (39.9% vs. 10.5%, p<.0001) and clinical remission (51.5% vs. 19.8%, p<0.0001) using DAS28-ESR at 24 weeks; CDAI and SDAI findings were similar
  
  • ACR20 (65% vs. 49%, p=0.0038; ACR50 and ACR70 were similar)

• Tocilizumab did not differ from adalimumab in HAQ-DI improvement and most other patient reported outcomes
IL-6-Inhibitors- Sarilumab

- One head to head RCT was identified of sarilumab monotherapy versus adalimumab monotherapy

- Sarilumab was superior to adalimumab in achieving:
  - Low disease activity (42.9% vs. 14.1%, p<0.0001) and clinical remission (26.6% vs. 7%, p<0.0001) using DAS28-ESR at 24 weeks; CDAI was similar
  - ACR20 (72% vs. 58%; p=0.0074; ACR50 and ACR70 were similar)
  - HAQ-DI improvement (patients achieving MCID of 0.3: 62% vs. 47.6%, all p<0.01)
JAK-inhibitors- Tofacitinib

• One head to head RCT was identified of tofacitinib vs. adalimumab (both in combination with methotrexate)

• Tofacitinib was similar to adalimumab in rates of remission, ACR response, and improvement in HAQ-DI and other patient reported outcomes at 24 weeks
JAK-inhibitors-Baricitinib

• 1 head-to-head RCT of baricitinib + methotrexate vs. adalimumab + methotrexate

• Baricitinib was superior to adalimumab in achieving:
  • **Disease Activity/Remission:** no differences in low disease activity and clinical remission at week 24; at week 52, baricitinib significantly more low disease activity (CDAI, SDAI, DAS28-ESR) but not remission
  • **ACR Response:** ACR20 (74% vs. 66%; p≤0.05) and ACR70 response (30% vs. 22%; p≤0.05) at Week 24; ACR50 not significantly different
  • **HAQ-DI:** 73% vs. 64% achieved MCID; p<0.05

• There were no significant differences in radiographic progression at week 52
TNFα-Inhibitors- Adalimumab monotherapy

• 2 head-to-head RCTs: sarilumab vs. adalimumab and tocilizumab vs. adalimumab

• **Disease Activity/Remission**: Less remission with adalimumab using DAS28-ESR at 24 weeks
  • Sarilumab (7% vs. 27%, p≤0.0001)
  • Tocilizumab (10.5% vs. 39.9%, p<0.0001)

• **ACR Response**: Less response with adalimumab
  • Sarilumab (ACR20 58% vs. 72%, p=0.0074), ACR50 & ACR70 were similar
  • Tocilizumab (ACR20 49% vs. 65%, p=0.0038), ACR50 & ACR70 were similar

• **HAQ-DI**: Adalimumab and tocilizumab similar improvement
  • Less improvement than sarilumab (47.6% vs. 62% for MCID of 0.3, p<0.01)
TNFα-Inhibitors - Adalimumab Combination Therapy

• 5 head-to-head RCTs identified

• Similar to abatacept, etanercept, tofacitinib, and certolizumab pegol in rates of remission, ACR response, and improvement in HAQ-DI

• No statistical differences between abatacept and adalimumab or baricitinib and adalimumab in slowing radiographic progression

• Adalimumab inferior to baricitinib for ACR20 and ACR70, and HAQ-DI; evidence mixed for disease activity/remission
TNFα-Inhibitors- Certolizumab Pegol

• 1 head-to-head RCT of certolizumab pegol + methotrexate vs. adalimumab + methotrexate

• No difference between agents in low disease activity, remission, ACR response, or HAQ-DI over 104 weeks of follow-up
TNFα-Inhibitors- Etanercept

• 1 head-to-head RCT identified of etanercept + DMARD vs. adalimumab + DMARD

• Mean change in disease activity (DAS28-CRP) comparable

• Data on other key outcomes not reported
TNFα-Inhibitors- Infliximab

• 1 head-to-head RCT of infliximab + methotrexate vs. abatacept (iv) + methotrexate

• No statistical differences in the proportion of patients with low disease activity, clinical remission, or change in HAQ-DI at week 24.

• Fewer patients achieved ACR20 at year 1 with IFX (56% vs 72%; p≤0.05); statistical differences not detected for ACR50 and 70.
Important Patient-reported Outcomes

• **Quality of life**: Statistically significant differences in Physical Component Score (SF-36) favoring TIM treatment over DMARD consistently reported,
  - 45-76% of patients met or exceeded an MCID of 5 across studies.
  - Changes in Mental Component Score were more moderate, and did not consistently report significant differences between TIMs and DMARDs.

• **Pain**: Statistically-significantly greater improvement with TIMs vs. DMARDs
  - 21.8 - 40.9 point improvement vs. 7.3 - 15.7 points (0-100 VAS scale)

• **Fatigue**: Statistically significant differences favoring treatment with a TIM over DMARD in all trials that reported on the FACIT-F.
  - 6.5-10.1 point improvement with a TIM vs. 2.2-point worsening to a 7.9-point improvement with DMARDs
Productivity

- Limited evidence

- Abatacept (sc) and adalimumab + methotrexate: similar improvements in absenteeism, reduced on-the-job effectiveness, work productivity loss, and activity impairment over two years of follow-up.

- Baricitinib and adalimumab combination therapy showed similar 52-week improvements in daily activity and work productivity

- Evidence from trials that compared TIMs to DMARDs was inconsistent for productivity/work loss changes.
Healthcare utilization and Caregiver Burden

- Limited evidence
- Etanercept + methotrexate vs. DMARD showed comparable proportions of patients visiting ED or a rheumatologist over 128 weeks of follow-up
- Requirements for caregiver assistance declined more with etanercept combination therapy.
TIMs vs. DMARDs (TIM-experienced population)

- Data from TIM-experienced populations were limited to 5 of the 11 TIMs: Abatacept, baricitinib, rituximab, sarilumab, and tocilizumab
- Only combination therapy evaluated
- Similar to TIM naïve populations, all produced statistically significant improvement in
  - Disease activity and remission (DAS28 at 24 weeks)
  - ACR response (ACR 20, 50 & 70 at 24 weeks)
  - HAQ-DI function and disability
Evidence from Observational Studies

• 3 registry studies compared adalimumab, etanercept, and infliximab

• CORRONA Registry: no significant differences in clinical remission or ACR response

• Hellenic Registry: No significant differences in rates of remission using DAS28-ESR, but greater remission with adalimumab using CDAI and SDAI definitions
  • CDAI: 15%[ADA] vs. 8% [IFX] vs. 7% [ETN], p=0.022
  • SDAI: 17% [ADA] vs. 8% [IFX] vs. 8% [ETN], p=0.009

• DANBIO Registry
  • Greater remission with adalimumab vs. infliximab (39% vs. 27%)
  • Greater ACR70 response for adalimumab (OR=2.05; 95% CI 1.52 to 2.76) and etanercept (OR=1.78; 95% CI 1.28-2.50) relative to infliximab
Network Meta-Analysis: Methods and Assumptions

• Assumptions
  • All conventional DMARDs have equivalent efficacy
  • Different types of administration of the same agents (i.e., iv vs. sc) may have differential performance
  • Incremental treatment effect is the same regardless of the ACR cut-off (i.e., 20 vs. 50 vs. 70)
• Random effects, multinomial likelihood model
• ACR20/50/70 response outcomes tabulated to create numbers of patients in mutually exclusive categories
• WinBUGS v1.4.3
Network Meta-Analysis Derived Proportions of Patients in Each ACR Response Category, by Combination Regimen: Mixed Population

<table>
<thead>
<tr>
<th>Treatment</th>
<th>ACR &lt;20</th>
<th>ACR 20-50</th>
<th>ACR 50-70</th>
<th>ACR 70-100</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etanercept + cDMARD</td>
<td>29%</td>
<td>23%</td>
<td>21%</td>
<td>27%</td>
</tr>
<tr>
<td>Certolizumab pegol + cDMARD</td>
<td>29%</td>
<td>23%</td>
<td>21%</td>
<td>26%</td>
</tr>
<tr>
<td>Tocilizumab (iv) + cDMARD</td>
<td>38%</td>
<td>23%</td>
<td>19%</td>
<td>19%</td>
</tr>
<tr>
<td>Sarilumab + cDMARD</td>
<td>40%</td>
<td>23%</td>
<td>19%</td>
<td>18%</td>
</tr>
<tr>
<td>Golimumab (sc) + cDMARD</td>
<td>41%</td>
<td>23%</td>
<td>18%</td>
<td>17%</td>
</tr>
<tr>
<td>Abatacept (iv) + cDMARD</td>
<td>42%</td>
<td>23%</td>
<td>18%</td>
<td>17%</td>
</tr>
<tr>
<td>Golimumab (iv) + cDMARD</td>
<td>42%</td>
<td>23%</td>
<td>18%</td>
<td>17%</td>
</tr>
<tr>
<td>Baricitinib + cDMARD</td>
<td>42%</td>
<td>23%</td>
<td>18%</td>
<td>16%</td>
</tr>
<tr>
<td>Tocilizumab (sc) + cDMARD</td>
<td>43%</td>
<td>23%</td>
<td>18%</td>
<td>16%</td>
</tr>
<tr>
<td>Abatacept (sc) + cDMARD</td>
<td>43%</td>
<td>23%</td>
<td>18%</td>
<td>16%</td>
</tr>
<tr>
<td>Infliximab + cDMARD</td>
<td>45%</td>
<td>23%</td>
<td>17%</td>
<td>15%</td>
</tr>
<tr>
<td>Adalimumab + cDMARD</td>
<td>45%</td>
<td>23%</td>
<td>17%</td>
<td>15%</td>
</tr>
<tr>
<td>Tofacitinib + cDMARD</td>
<td>47%</td>
<td>23%</td>
<td>17%</td>
<td>14%</td>
</tr>
<tr>
<td>Rituximab + cDMARD</td>
<td>48%</td>
<td>23%</td>
<td>16%</td>
<td>13%</td>
</tr>
<tr>
<td>Intensive cDMARD*</td>
<td>50%</td>
<td>23%</td>
<td>16%</td>
<td>12%</td>
</tr>
<tr>
<td>Conventional DMARD</td>
<td>73%</td>
<td>16%</td>
<td>8%</td>
<td>4%</td>
</tr>
</tbody>
</table>

*combination therapy with 2-3 conventional DMARDs
### Network Meta-Analysis Derived Proportions of Patients in Each ACR Response Category, by Monotherapy Regimen: Mixed Population

<table>
<thead>
<tr>
<th>Treatment</th>
<th>ACR &lt;20</th>
<th>ACR 20-50</th>
<th>ACR 50-70</th>
<th>ACR 70-100</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tocilizumab (iv)</td>
<td>25%</td>
<td>24%</td>
<td>21%</td>
<td>30%</td>
</tr>
<tr>
<td>Etanercept</td>
<td>27%</td>
<td>24%</td>
<td>20%</td>
<td>28%</td>
</tr>
<tr>
<td>Sarilumab</td>
<td>28%</td>
<td>25%</td>
<td>20%</td>
<td>27%</td>
</tr>
<tr>
<td>Adalimumumab</td>
<td>43%</td>
<td>25%</td>
<td>16%</td>
<td>16%</td>
</tr>
<tr>
<td>Conventional DMARD</td>
<td>70%</td>
<td>18%</td>
<td>8%</td>
<td>4%</td>
</tr>
</tbody>
</table>
Network Meta-Analysis: TIM-experienced population

- RTX + DMARD
- ABT (iv) + DMARD
- TCZ (iv) + DMARD
- SAR + DMARD
- BAR + DMARD

Connections:
- RTX + DMARD to DMARD: 1
- ABT (iv) + DMARD to DMARD: 1
- TCZ (iv) + DMARD to DMARD: 1
- DMARD to SAR + DMARD: 2
- DMARD to BAR + DMARD: 3
≥ACR20, TIM-experienced Population

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Point Estimate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TCZ (IV)+cDMARD</td>
<td>74.3 (47.4, 91.4)</td>
</tr>
<tr>
<td>RTX+cDMARD</td>
<td>56.6 (30, 80.4)</td>
</tr>
<tr>
<td>ABT (IV)+cDMARD</td>
<td>52.3 (25.5, 77.7)</td>
</tr>
<tr>
<td>SAR+cDMARD</td>
<td>46.7 (22.3, 72.4)</td>
</tr>
<tr>
<td>BAR+cDMARD</td>
<td>43.1 (19.1, 70.1)</td>
</tr>
<tr>
<td>cDMARD</td>
<td>22.6 (8, 46)</td>
</tr>
</tbody>
</table>
Network Meta-Analysis Derived Proportions of Patients in each ACR Response Category, by Regimen: TIM-experienced Population

<table>
<thead>
<tr>
<th>Treatment</th>
<th>ACR &lt;20</th>
<th>ACR 20-50</th>
<th>ACR 50-70</th>
<th>ACR 70-100</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tocilizumab (iv) + DMARD</td>
<td>38%</td>
<td>24%</td>
<td>19%</td>
<td>19%</td>
</tr>
<tr>
<td>Rituximab + DMARD</td>
<td>42%</td>
<td>24%</td>
<td>18%</td>
<td>17%</td>
</tr>
<tr>
<td>Abatacept (iv) + DMARD</td>
<td>46%</td>
<td>23%</td>
<td>17%</td>
<td>14%</td>
</tr>
<tr>
<td>Sarilumab + DMARD</td>
<td>52%</td>
<td>22%</td>
<td>15%</td>
<td>11%</td>
</tr>
<tr>
<td>Baricitinib + DMARD</td>
<td>56%</td>
<td>21%</td>
<td>13%</td>
<td>9%</td>
</tr>
<tr>
<td>Conventional DMARD</td>
<td>77%</td>
<td>14%</td>
<td>6%</td>
<td>3%</td>
</tr>
</tbody>
</table>
Long-term Cost Effectiveness
Appendix Slides
## Model Cohort Characteristics (base-case)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age</td>
<td>55 years (range 50 to 60 years old)</td>
<td>Curtis et al., 2010</td>
</tr>
<tr>
<td>Female</td>
<td>79% (range 73% to 86%)</td>
<td>Curtis et al., 2010</td>
</tr>
<tr>
<td>Caucasian</td>
<td>84%</td>
<td>Curtis et al., 2010</td>
</tr>
<tr>
<td>Mean Weight</td>
<td>170 pounds</td>
<td>Frayer et al., 2012 (National Health and Nutrition Examination Survey data)</td>
</tr>
<tr>
<td>Baseline HAQ</td>
<td>1.7 (range: 1.37 to 2.03)</td>
<td>Curtis et al., 2010</td>
</tr>
<tr>
<td>Baseline mTSS</td>
<td>54 (SD: 64)</td>
<td>Lillegraven et al., 2012</td>
</tr>
</tbody>
</table>
# Model Cohort Characteristics for TIM Experienced Population

<table>
<thead>
<tr>
<th></th>
<th>Value</th>
<th>Primary Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age</td>
<td>57 years</td>
<td>Pappas et al, 2014</td>
</tr>
<tr>
<td>Female</td>
<td>79.9%</td>
<td>Pappas et al, 2014</td>
</tr>
<tr>
<td>Caucasian</td>
<td>83.9%</td>
<td>Pappas et al, 2014</td>
</tr>
<tr>
<td>Mean weight</td>
<td>170 lbs.</td>
<td>National Health and Nutrition Examination Survey</td>
</tr>
<tr>
<td>Baseline HAQ prior to cDMARD treatment benefit</td>
<td>1.79</td>
<td>Calculation (weighted average from biologic-experienced trials)</td>
</tr>
<tr>
<td>Baseline mTSS</td>
<td>93</td>
<td>Barnabe et al, 2012</td>
</tr>
</tbody>
</table>
## Scenario Analysis Results: TIM
### Experienced Population versus Mixed Population

<table>
<thead>
<tr>
<th></th>
<th>ICER (biologic experienced population)</th>
<th>ICER (mixed population)</th>
</tr>
</thead>
<tbody>
<tr>
<td>rituximab</td>
<td>$196,634</td>
<td>$231,965</td>
</tr>
<tr>
<td>abatacept (iv)</td>
<td>$193,664</td>
<td>$220,523</td>
</tr>
<tr>
<td>tocilizumab (iv)</td>
<td>$189,370</td>
<td>$213,221</td>
</tr>
</tbody>
</table>
## Contributions of ACR and mTSS to HAQ, for TIMs Added on to Conventional DMARD

<table>
<thead>
<tr>
<th>Treatment 1</th>
<th>Average Proportion of HAQ Contribution from ACR</th>
<th>Average Proportion of HAQ Contribution from mTSS</th>
</tr>
</thead>
<tbody>
<tr>
<td>rituximab</td>
<td>92.1%</td>
<td>7.9%</td>
</tr>
<tr>
<td>abatacept (iv)</td>
<td>94.5%</td>
<td>5.5%</td>
</tr>
<tr>
<td>abatacept (sc)</td>
<td>92.4%</td>
<td>7.6%</td>
</tr>
<tr>
<td>tocilizumab (iv)</td>
<td>91.1%</td>
<td>8.9%</td>
</tr>
<tr>
<td>tocilizumab (sc)</td>
<td>91.4%</td>
<td>8.6%</td>
</tr>
<tr>
<td>tofacitinib</td>
<td>95.7%</td>
<td>4.3%</td>
</tr>
<tr>
<td>adalimumab</td>
<td>93.4%</td>
<td>6.6%</td>
</tr>
<tr>
<td>certolizumab pegol</td>
<td>94.6%</td>
<td>5.4%</td>
</tr>
<tr>
<td>etanercept</td>
<td>88.9%</td>
<td>11.1%</td>
</tr>
<tr>
<td>golimumab (sc)</td>
<td>96.7%</td>
<td>3.3%</td>
</tr>
<tr>
<td>golimumab (iv)</td>
<td>93.2%</td>
<td>6.8%</td>
</tr>
<tr>
<td>infliximab</td>
<td>89.8%</td>
<td>10.2%</td>
</tr>
</tbody>
</table>
Cost-Effectiveness Frontier for TIMs Added on to Conventional DMARD

[Cost-Effectiveness Frontier Graph]

- adalimumab
- certolizumab pegol
- etanercept
- golimumab (sc)
- golimumab (iv)
- infliximab
- rituximab
- abatacept (sc)
- tocilizumab (iv)
- tocilizumab (sc)
- abatacept (iv)
- tofacitinib
- cDMARD
Comparisons to the TIM Market Leader; all TIMs added on to Conventional DMARD