PERSONALIZED MEDICINE IN RHEUMATOLOGY: OPTIMIZING THE TREATMENT OF RHEUMATOID ARTHRITIS

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Acknowledgements & Disclosures

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- National Institutes of Health

Research Grants (to UAB) & Consulting
Janssen, Amgen, Abbott, UCB, CORRONA, Crescendo, BMS, Roche/Genentech, Pfizer, Celgene
Outline

• Description of Rheumatoid Arthritis (RA)
• Impact of RA
  – Clinical
  – Economic
• Management of RA
• Measurement of RA Disease Activity
  – Clinical
  – Biomarkers
• The Future

Worldwide Impact of TNF Inhibitors*

<table>
<thead>
<tr>
<th></th>
<th>Treated in Pivotal Trials</th>
<th>Worldwide Rxns 2005</th>
<th>Sales 2005 (billions)</th>
<th>Sales 2010 (billions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etanercept</td>
<td>1272</td>
<td>376,000</td>
<td>$3.6</td>
<td>$8.4</td>
</tr>
<tr>
<td>Infliximab</td>
<td>1372</td>
<td>700,000</td>
<td>$2.5</td>
<td>$7.4</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>2468</td>
<td>150,000</td>
<td>$1.4</td>
<td>$6.5</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>5112</strong></td>
<td><strong>1,226,000</strong></td>
<td><strong>$7.5</strong></td>
<td><strong>$22.3</strong></td>
</tr>
</tbody>
</table>

* Sales and use data from manufacturers website, press releases (Amgen.com; Wyeth.com; Abbott.com; Centocor.com). Pivotal trial #s from product labeling
Top Selling Drugs in the U.S., 2013

<table>
<thead>
<tr>
<th>Rank</th>
<th>Drug, Company</th>
<th>Retail Sales, $</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Abilify, Otsuka</td>
<td>6,293,801,000</td>
</tr>
<tr>
<td>2</td>
<td>Nexium, AstraZeneca</td>
<td>5,974,550,000</td>
</tr>
<tr>
<td>3</td>
<td>Humira, AbbVie</td>
<td>5,428,479,000</td>
</tr>
<tr>
<td>4</td>
<td>Crestor, AstraZeneca</td>
<td>5,195,930,000</td>
</tr>
<tr>
<td>5</td>
<td>Cymbalta, Eli Lilly</td>
<td>5,083,111,000</td>
</tr>
<tr>
<td>6</td>
<td>Advair Diskus, GSK</td>
<td>4,981,108,000</td>
</tr>
<tr>
<td>7</td>
<td>Enbrel, Amgen</td>
<td>4,585,701,000</td>
</tr>
<tr>
<td>8</td>
<td>Remicaide, Centocor</td>
<td>3,980,556,000</td>
</tr>
<tr>
<td>9</td>
<td>Copaxone, Teva</td>
<td>3,603,958,000</td>
</tr>
<tr>
<td>10</td>
<td>Neulasta, Amgen</td>
<td>3,472,969,000</td>
</tr>
<tr>
<td>11</td>
<td>Rituxan, Genentech</td>
<td>3,208,525,000</td>
</tr>
</tbody>
</table>

Drugs.com, updated February 2014

Defining RA

- RA is a systemic, inflammatory polyarthritis that leads to joint destruction, deformity, and loss of function.
- RA produces inflammation of the synovial membranes and periarticular structures that results in:
  - Pain
  - Swelling
  - Stiffness
  - Functional limitation
  - Pannus formation
  - Erosive damage to bone and cartilage
  - Deformity

ACR Criteria for Classification of RA

Must be present for ≥6 weeks
- Morning stiffness ≥1 hour
- Simultaneous polyarthritis (>3 joints involved)
- Arthritis of hand joints, MCPs, PIPs, wrists
- Symmetric polyarthritis
- Rheumatoid nodules
- Abnormal titer of serum rheumatoid factor
- Radiographic evidence of RA in hand or wrist

*Diagnosis requires at least 4 of 7 criteria.


Risk Factors for RA

<table>
<thead>
<tr>
<th>Risk Factors for Developing RA</th>
<th>Modifiable Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-Modifiable Factors</td>
<td></td>
</tr>
<tr>
<td>- Female sex *</td>
<td>Smoking (Tobacco)*</td>
</tr>
<tr>
<td>- Age *</td>
<td>Obesity</td>
</tr>
<tr>
<td>- Genetics*</td>
<td>Poor dentition</td>
</tr>
<tr>
<td>- Family history</td>
<td></td>
</tr>
<tr>
<td>- Seropositivity (RF, CCP)*</td>
<td></td>
</tr>
</tbody>
</table>

* Also associated with disease severity

Features Associated with Extra-Articular Disease
- Long-standing RA
- Rheumatoid nodules
- High titer RF+, CCP+
- Antinuclear antibodies

RF=rheumatoid factor; CCP=cyclic citrullinated peptide

**Clinical Features of RA**

<table>
<thead>
<tr>
<th>Articular</th>
<th>Constitutional</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morning stiffness</td>
<td>Fatigue</td>
</tr>
<tr>
<td>Polyarthritis (symmetric)</td>
<td>Anorexia</td>
</tr>
<tr>
<td>Joint swelling and tenderness</td>
<td>Weight loss</td>
</tr>
<tr>
<td>PIP, MCP, wrist, MTP involvement</td>
<td>Fever</td>
</tr>
<tr>
<td>Limitation of motion</td>
<td>Myalgia</td>
</tr>
<tr>
<td>Joint misalignment</td>
<td>Anemia</td>
</tr>
</tbody>
</table>

**RA vs Osteoarthritis (OA)**

<table>
<thead>
<tr>
<th>OA</th>
<th>Feature</th>
<th>RA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spine, knee, hip, MTPs</td>
<td>Other typical joints</td>
<td>Knees, ankles, MTPs, hips</td>
</tr>
<tr>
<td>All-day gel phenomenon</td>
<td>Stiffness</td>
<td>Prominent AM stiffness</td>
</tr>
<tr>
<td>Worse with activity</td>
<td>Pain</td>
<td>Improves with activity</td>
</tr>
<tr>
<td>Bony</td>
<td>Swelling</td>
<td>Synovial, effusion, tendon</td>
</tr>
<tr>
<td>Normal</td>
<td>ESR, CRP, RF, CCP</td>
<td>Abnormal or elevated</td>
</tr>
<tr>
<td>Sclerosis, osteophytes</td>
<td>Radiographs</td>
<td>Erosions, osteopenia</td>
</tr>
</tbody>
</table>
The Pathogenesis of RA

NORMAL

RHEUMATOID ARTHRITIS

Synovial membrane

Cartilage

Capsule

Inflamed synovial membrane

Major cell types: T lymphocytes, macrophages

Minor cell types: fibroblasts, plasma cells, endothelium, dendritic cells

Pannus

Synovial fluid

Major cell type: neutrophils

Cartilage Thinning


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RA—Spectrum of Disease Activity

Early

Intermediate

Severe

Images courtesy of J. Cush.
Ulnar deviation mcp subluxation

Symmetric Polyarthritis—Swan-Neck Deformity
Rheumatoid Deformities

- Swan-neck deformity
- Boutonniere deformity
- Ulnar drift (at MCPs)
- Zeta deformity of thumb
- Piano-key deformity
- Bent-fork deformity
- Arthritis mutilans
- Hallux valgus
- Hammer toes

Images courtesy of J. Cush.
Extra-Articular Features

- Hematologic
  - Anemia
  - Thrombocytosis
  - Felty’s syndrome

- Ocular
  - Sjogren’s syndrome
  - Episcleritis, scleritis

- Pulmonary
  - Interstitial lung disease
  - Pleural effusions
  - Pulmonary nodules

- Neurologic
  - Peripheral neuropathy
  - Cervical myelopathy
  - Mononeuritis multiplex

- Vascular
  - Vasculitis
  - Ischemic ulcers

Swan-Neck or Boutonniere Deformity?
Erosions lead to functional loss and disability: Goal is to manage to radiographic remission

Erosion
• Bone damage

Joint Space Narrowing
• Soft tissue damage

Inflammatory Cascade of RA: Links of a Chain

APCs
T cells
B cells
Cytokines
RA

Activates
T

Activates
B

Activates
RF Autoantibodies

Proteases and Cytokines

Inflammation and Joint damage
Cumulative Inflammation Is Damaging: Goal Is to Manage Patients to Clinical Remission

- RA Inflammation Begets
  - Tissue damage
  - Bone destruction
  - Atherosclerosis, CV disease
  - Early mortality

Ref adapted from: Steve Paget, Hosp Special Surgery.

Widening Mortality Gap in RA

Mortality rates have declined for the general population but remain high for RA

### Annual Indirect Costs\(^a\) For Employees With and Without RA

<table>
<thead>
<tr>
<th></th>
<th>Employees with RA</th>
<th>Employees without RA</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sick leave</td>
<td>$470</td>
<td>$325</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Short-term disability</td>
<td>$466</td>
<td>$218</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Long-term disability</td>
<td>$55</td>
<td>$14</td>
<td>.0505</td>
</tr>
<tr>
<td>Workers’ compensation</td>
<td>$271</td>
<td>$181</td>
<td>.0093</td>
</tr>
<tr>
<td><strong>Total (sum above)</strong></td>
<td><strong>$1,262</strong></td>
<td><strong>$737(^b)</strong></td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) Adjusted mean.

\(^b\) Difference due to rounding

Kleiman NL, Brook RA, Kirback SE, Cifaldi MA. Work Absences and Costs Associated With Rheumatoid Arthritis: A Comparison Between Employees With and Without Rheumatoid Arthritis in a United States Population. Presented at the American College of Rheumatology Annual Scientific Meeting, November 4–9, 2011, Chicago, IL.

### Work Disability Associated With RA

Significant Costs Associated with RA

- Estimated annual RA related direct cost in 2001 - $9,519 per patient and in 2006 - $11,404
  - Likely even higher today, especially with biologic use increasing
- Direct costs may be underestimated as they don’t account for RA associated co-morbidities
  - CVD increases cost $2,741
  - Depression increases cost $2,109
- Societal Cost
  - 53% less likely to be employed, 3.6 times as many sick days
  - Increased rates of disability
  - 9.6% of patients ≤ 65 years receive social security disability


Higher Disease Activity Associated with Increased Direct Cost

**Direct Costs* Associated with Achieving Different Disease Activity States**

- First 6 Months: $1,098
- Second 6 Months: $728
- Annual Cost: $1,731

*B Converted to dollars; $1=0.7 €

Summary: a diagnosis of rheumatoid arthritis (RA) triggers a challenging and uncertain future

- 1.5 + million patients, over 100,000 new cases/year
- Average age at diagnosis in mid to late 40’s
- Significant bone erosions, cartilage degradation, and deformity
- Extra-articular features and associated co-morbidities (e.g. CVD, stroke)
- Chronic systemic inflammation
- Quality of life issues, disability, long term costs
- Life expectancy lowered by over 5 years

Therapeutics that treat inflammatory conditions such as RA had the highest PMPY spend in 2012

<table>
<thead>
<tr>
<th>Therapy Class</th>
<th>PMPY Spend</th>
<th>Utilization Trend</th>
<th>Unit Cost Trend</th>
<th>Total Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inflammatory Conditions</td>
<td>$50.62</td>
<td>9%</td>
<td>14.0%</td>
<td>23.0%</td>
</tr>
<tr>
<td>Multiple Sclerosis</td>
<td>$37.98</td>
<td>0.5%</td>
<td>17.3%</td>
<td>17.8%</td>
</tr>
<tr>
<td>Cancer</td>
<td>$31.98</td>
<td>3.4%</td>
<td>22.3%</td>
<td>25.8%</td>
</tr>
<tr>
<td>HIV</td>
<td>$20.78</td>
<td>-2.1%</td>
<td>11.1%</td>
<td>9.0%</td>
</tr>
<tr>
<td>Hep C</td>
<td>$7.82</td>
<td>28.9%</td>
<td>4.8%</td>
<td>33.7%</td>
</tr>
<tr>
<td>Growth Deficiency</td>
<td>$7.41</td>
<td>1.7%</td>
<td>7.7%</td>
<td>9.5%</td>
</tr>
<tr>
<td>Anticoagulants</td>
<td>$6.74</td>
<td>1.7%</td>
<td>0.3%</td>
<td>2.1%</td>
</tr>
<tr>
<td>Pulmonary Hypertension</td>
<td>$5.71</td>
<td>5.1%</td>
<td>6.2%</td>
<td>11.3%</td>
</tr>
<tr>
<td>Respiratory Conditions</td>
<td>$5.56</td>
<td>1.5%</td>
<td>25.7%</td>
<td>27.2%</td>
</tr>
<tr>
<td>Transplant</td>
<td>$4.92</td>
<td>2.2%</td>
<td>-6.9%</td>
<td>-4.7%</td>
</tr>
<tr>
<td>Other</td>
<td>$27.68</td>
<td>-24.9%</td>
<td>43.7%</td>
<td>18.8%</td>
</tr>
<tr>
<td>Total</td>
<td>$207.19</td>
<td>-0.4%</td>
<td>18.7%</td>
<td>18.4%</td>
</tr>
</tbody>
</table>

Source: Express Scripts 2012 drug trend report
MANAGEMENT OF RA

Biologics and Non-Biologic DMARDs used in RA

<table>
<thead>
<tr>
<th>Biologics</th>
<th>Non-Biologics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-TNF</td>
<td>Methotrexate</td>
</tr>
<tr>
<td>Adalimumab (Humira)</td>
<td>Sulfasalazine (SSZ)</td>
</tr>
<tr>
<td>Certolizumab (Cimzia)</td>
<td>Hydroxychloroquine (HCQ)</td>
</tr>
<tr>
<td>Etanercept (Enbrel)</td>
<td>Leflunomide (LEF)</td>
</tr>
<tr>
<td>Golimumab (Simponi)</td>
<td>Gold</td>
</tr>
<tr>
<td>Infliximab (Remicade)</td>
<td>Minocycline</td>
</tr>
<tr>
<td>B-cell depleting therapies</td>
<td>Azathioprine</td>
</tr>
<tr>
<td>Rituximab (Rituxan)</td>
<td>Tofacitinib (Xeljanz)</td>
</tr>
<tr>
<td>IL-1Ra</td>
<td></td>
</tr>
<tr>
<td>Anakinra (Kineret)</td>
<td></td>
</tr>
<tr>
<td>IL-6Ra</td>
<td></td>
</tr>
<tr>
<td>Tocilizumab (Actemra)</td>
<td></td>
</tr>
<tr>
<td>T-cell costimulatory inhibitors</td>
<td></td>
</tr>
<tr>
<td>Abatacept (Orencia)</td>
<td></td>
</tr>
</tbody>
</table>

DMARD = disease modifying anti-rheumatic drug
2012 Update of the 2008 American College of Rheumatology Recommendations for the Use of Disease-Modifying Antirheumatic Drugs and Biologic Agents in the Treatment of Rheumatoid Arthritis

JASVINDER A. SINGH,1 DANIEL E. FURST,2 ASEEM BHARAT,1 JEFFREY R. CURTIS,1 ARTHUR F. KAVANAUGH,3 JOEL M. KREMER,4 LARRY W. MORELAND,3 JAMES O’DELL,5 KEVIN L. WINTHROP,7 TIMOTHY BEUKELMAN,1 S. LOUIS BRIDGES JR.,1 W. WINN CHATHAM,1 HAROLD E. PAULUS,2 MARIA SUAREZ-ALMAZOR,6 CLAIRE BOMBARDIER,9 MAXIME DOUGADOS,10 DINESH KHANNA,11 CHARLES M. KING,12 AMYE L. LEONG,7 ERIC L. MATTESON,14 JOHN T. SCHOUHBOE,15 EILEEN MOYNIHAN,16 KAREN S. KOLRA,17 ARCHANA JAIN,1 ELIZABETH R. VOLKEMANN,2 HARSHI AGRAWAL,9 SANGMEE BAE,9 AMY S. MUDANO,1 NIVEDITA M. PATKAR,4 AND KENNETH G. SAAG2

![Diagram showing 2012 ACR Recommendations for Early RA (< 6 months)](image-url)
Figure 2: Established RA

Management of Established RA from the 2012 ACR Recommendations

Key management parameters
• Features of Poor Prognosis
• Response to prior RA treatments
• Disease Activity

Prevalence of Biologic Use in U.S. Medicare Beneficiaries with RA

Overall prevalence of biologic use ~30%; higher in some health plans

Infliximab accounted for more than $440 million spent by Medicare in 2009

Prevalence (%) of Current Biologic Users

Zhang J, Arthritis Care Res; 2013 epub ahead of print
Evidence based guidelines require clear definitions of disease activity to make rational therapeutic choices, but it is not possible or appropriate to mandate use of a single disease activity score for the individual physician...
Tools to manage RA are imprecise, incomplete, and inadequate

<table>
<thead>
<tr>
<th>Measurement Tools</th>
<th>Issues</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rheumatoid Factor (RF)</td>
<td>Used in diagnosis, not appropriate for ongoing management</td>
</tr>
<tr>
<td>Anti-CCP</td>
<td>Used in diagnosis, one time patient stratification</td>
</tr>
<tr>
<td>Disease Activity Indices (DAS28, CDAI, SDAI)</td>
<td>Composite tools that rely on subjective measures (SJC, patient assessment) and non-specific inflammatory measures. Don't discriminate well in patients with low levels of disease. Time consuming for community practices.</td>
</tr>
<tr>
<td>ESR, CRP</td>
<td>Non specific markers of inflammation</td>
</tr>
<tr>
<td>X-ray</td>
<td>Annual radiographic exam, look-back at damage</td>
</tr>
<tr>
<td>MRI, US</td>
<td>More sensitive than x-ray, but expensive, not widely available</td>
</tr>
<tr>
<td>Patient reported outcomes</td>
<td>Subjective, self-reported</td>
</tr>
<tr>
<td>(HAQ, SF36, Patient Global)</td>
<td></td>
</tr>
</tbody>
</table>

What We CAN Measure

- Formal joint counts
- Patient global assessment*
- Physician global assessment
- HAQ/MDHAQ*
- Categorical outcomes measures
  - ACR 20, 50, 70*
- Continuous measurement tools
  - DAS*
  - SDAI*
  - CDAI*
  - GAS*
  - SF-36*
  - RAPID*
- Imaging results (musculoskeletal ultrasound, MRI)
- Laboratory values
  ESR/CRP, RA, ACP/CCP

*Is or contains patient-reported outcome measures
Cush J. presented at the American College of Rheumatology meeting 2008.

What We DO Measure

![Bar Chart]

Validated Measures of Disease Activity Infrequently Used

<table>
<thead>
<tr>
<th>Measure</th>
<th>Percent Performing as Part of Routine RA Care (n=978)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morning Stiffness</td>
<td>88.8</td>
</tr>
<tr>
<td>Joint exam (complaint focused)</td>
<td>72.8</td>
</tr>
<tr>
<td>ESR</td>
<td>68.1</td>
</tr>
<tr>
<td>CRP</td>
<td>51.8</td>
</tr>
<tr>
<td>Patient Global VAS</td>
<td>45.3</td>
</tr>
<tr>
<td>Patient Pain VAS</td>
<td>43.7</td>
</tr>
<tr>
<td>Physician Global Assessment</td>
<td>41.5</td>
</tr>
<tr>
<td>28 Joint Count</td>
<td>27.1</td>
</tr>
<tr>
<td>66 Joint Count</td>
<td>18.8</td>
</tr>
<tr>
<td>HAQ (unscored)</td>
<td>17.7</td>
</tr>
<tr>
<td>HAQ (scored)</td>
<td>12.3</td>
</tr>
<tr>
<td>DAS (any)</td>
<td>6</td>
</tr>
<tr>
<td>ACR20 or ACR-n</td>
<td>1.8</td>
</tr>
</tbody>
</table>

Cush J. Ann Rheum Dis 2005;64(iv18–iv23.)
Tight Control Trends

- Treat to target
  - If not in LDAS or remission adjust treatment

- Treat to response
  - If response is not achieved adjust treatment (CAMERA, DREAM)

- Quantitative measures of response play an important role

- Clinical vs. radiologic response

- Time to remission is important to outcomes
  - Time to remission predicts sustained DAS remission

Measurement and Tight Control: Improved Outcomes

- Diabetes and Hemoglobin A1C (target < 7%)
  - In both type I and II diabetes proven to reduce microvascular and neuropathic complications
  - Some studies & meta-analysis have also shown reduction in CVD

- CVD and hypertension (target 140/90 mm Hg)
  - Demonstrated to reduce cardiovascular events, MI, stroke, and death
  - Demonstrated to protect against renal sequelae

- CHD and hypercholesterolemia (targets - very high risk < LDL-C < 70 mg/dL, high risk < 100 mg/dL, moderately high risk < 130 mg/dL)
  - Reduces risk of major vascular events, coronary death, non-fatal MI, stroke, cardiovascular re-vascularization
Why Tight Control in RA?

• RA has immediate and cumulative effects
• Rapid joint damage early in disease
  – Rate of structural damage greatest during first 2 years
  – 75% of all joint damage occurs in first 5 years
• Joint damage is mostly irreversible
• Significant direct cost and societal costs

Principles of Tight Control in RA

• Treatment goal is remission
  – Debate over what constitutes remission (i.e. clinical, radiologic, disability, etc.) and what measure to use
  – 2011 ACR/EULAR definition, ≤ 1 SJ & TJ, ≤ 1 mg/L CRP and ≤1 Pt. Global or in clinical practice SDAI acceptable
  – Tight control studies generally use a clinical index for remission
• Adjust treatment at least every 3 months until disease under control
• Measure and document disease activity
  – As frequently as monthly in active patients
  – Less frequently, every 3-6 months for patient in sustained low disease activity or remission
**Principles of Tight Control in RA**

- **Treatment goal is remission**
  - 2011 ACR/EULAR definition, ≤ 1 SJ & TJ, CRP ≤ 1 mg/L and ≤ 1 Pt. Global (on a 0-10 scale)
  - Tight control studies generally use a clinical index for remission

- **Adjust treatment at least every 3 months until disease under control**

- **Measure and document disease activity**
  - As frequently as monthly in active patients
  - Less frequently, every 3-6 months for patient in sustained low disease activity or remission

---

**Tight Control Study Designs**

<table>
<thead>
<tr>
<th>Treatment Arms</th>
<th>Treatment Decision Target</th>
<th>Visit Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>FIN/Raco</td>
<td>MTX + SSZ + HCQ with prednisolone</td>
<td>Remission 1</td>
</tr>
<tr>
<td></td>
<td>Single DMARD +/- prednisolone</td>
<td></td>
</tr>
<tr>
<td>BeST</td>
<td>Sequential monotherapy</td>
<td>DAS44 ≤ 2.4</td>
</tr>
<tr>
<td></td>
<td>Step up combination</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Initial (DMARD) combination therapy with tapered</td>
<td></td>
</tr>
<tr>
<td></td>
<td>high dose prednisone</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Initial Combination therapy with MTX + IFX</td>
<td></td>
</tr>
<tr>
<td>TICORA</td>
<td>SSZ step up to combination DMARDs</td>
<td>DAS44 ≤ 2.4</td>
</tr>
<tr>
<td></td>
<td>DMARD mono +/- alternative DMARD mono or combo DMARD</td>
<td></td>
</tr>
<tr>
<td>CAMERA</td>
<td>Intensive: MTX step up to MTX + cyclosporine</td>
<td>Sustained Response 2 (using computer decision program to assess response)</td>
</tr>
<tr>
<td></td>
<td>Conventional: MTX step up to MTX + cyclosporine</td>
<td>Sustained Response 2</td>
</tr>
</tbody>
</table>

1. Remission defined as ≥5 of ACR criteria for remission excluding fatigue and duration of remission.
2. No swollen joint and ≥2 out of 3 criteria of pain (improvement), ESR ≤ 20 mm/hr and HAQ general well-being ≤ 0.2.

Sources:

Abbreviations: NS = not specified, HCQ = hydroxychloroquine, MTX = methotrexate, SSZ = sulfasalazine.
Tight Control Versus Standard of Care – Early RA, Primarily* Traditional DMARDs

Remission Rates: Tight Control vs. Standard of Care

* Higher remission rates with tight control using traditional DMARDs

FIN-Raco | BeSt* | TICORA | CAMERA
---|---|---|---
45% | 16% | 31% | 18%
65% | 16% | 50% | 37%

Tight Control vs. Standard of Care – Early RA, Primarily* Traditional DMARDs - Disability

Improvement in HAQ Tight Control vs. Standard of Care

* Tight control with traditional DMARDs results in greater reduction in disability as measured by the HAQ

Barriers to Tight Control

• Lack of routine measurement of disease activity
• Time constraints in busy clinical practices
• Lack of agreement of best measurement tool
• Inter- and intra- assessor variability of current measurement tools
• Misaligned quality metrics and physician incentives

Quality Incentive Not Aligned with Guidelines and Recommendations

• Medicare Physician Quality Reporting System only requires assessment of disease activity at least once per year
  – Once per year, not enough for most patients

• ACR treatment recommendations start with disease activity assessment to determine treatment options

• Treat-to-target guidelines recommend more frequent assessment
  – 1-3 months for active patients or every 3-6 months for remission or stable low disease activity patients
INADEQUACY OF CURRENT TOOLS

Challenges in Using Patient Reported Measures to measure RA disease activity

• Affected by non-RA factors
  – Stress
  – Age
  – Non-RA co-morbidities
  – Individual perception/tolerance of pain

• Early in disease may represent disease activity, but later in the disease may be reflecting joint damage
Challenges in Using Physician-Assessed Disease Activity Measures in RA

- **Clinician Joint Counts**
  - Inter-observer variability in SJC as high as 15 and variability of DAS28 score up to 0.92 on one study
  - Intra-observer variability - smallest detectable difference is 3.5 for SJC and 4.8 for TJC
  - TJC can be affected by non-RA related disease such as fibromyalgia

- **Laboratory Tests (ESR & CRP)**
  - Normal ESR in 45-47% and normal CRP in 44-58% RA patients
  - Data from clinical trials of an anti-TNF agent showed
    - 26.4% patients with 0 swollen joints had elevated ESR or CRP
    - Patients with active disease may have normal lab tests: 51% of patients with 1-4 SJC, and 29% of patients with > 4 swollen joints, had normal ESR and CRP respectively

SJC = swollen joint count, TJC = tender joint count


Physician Quality Reporting System (PQRS)

**Measure K: Periodic Assessment of Disease Activity**

**Measure Description**: All patients 18 years and older with a diagnosis of Rheumatoid Arthritis (RA)

**Technical Specifications**: Administrative Data

**Definition**: Defined as the number of patients with a diagnosis of RA who have had periodic assessment of their disease activity.

**Benefit of reporting**: Initially 2% bonus on Medicare part B revenues
Now fallen to 0.5%
2% penalty starting in 2014
Summary: Discordance between different RA disease activity assessments are well documented

- Physician and patient assessments are relatively subjective and may differ\(^1\)
  - Clinical Joint Assessments
    - TJC in context of fibromyalgia, nodal osteoarthritis
    - "Swollen joints" — fibrous thickening vs synovitis
  - Patient Global and PROs
    - Frequently affected by comorbid symptoms (headache, back pain)
    - Includes nonreversible functional impairment
  - HAQ/MDHAQ (disability)
    - Allows for irreversible disability (floor effect)
- Composite disease activity measures (e.g. DAS28, CDAI, SDAI, RAPID3) suffer from the same problems

\(^1\) Barton J, et. al. Arthritis Care & Research Vol. 62, No. 6, June 2010, pp 857–864

Global Assessments of Disease Activity

- Physician Global – based on their overall Gestalt

| 6. Physician’s Global Assessment (PGA): Where would you rate the subject’s Rheumatoid Arthritis (RA) disease activity? (Please check ONE box only) |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| 0  | 0.5 | 1.0 | 1.5 | 2.0 | 2.5 | 3.0 | 3.5 | 4.0 | 4.5 | 5.0 | 5.5 | 6.0 | 6.5 | 7.0 | 7.5 | 8.0 | 8.5 | 9.0 | 9.5 | 10 |
| No arthritis activity | | | | | | | | | | | | | | | | | | | | | | | | | Severe arthritis activity |

- Considering all the ways in which illness and health conditions may affect you at this time, please indicate below how you are doing:
  - VERY WELL
  - WELL
  - FAIR
  - POOR
  - VERY POOR

- Correlation of -0.172 in one study
- 36% discordance of more than 25 mm (2.5) in another
- Potential reasons may include non-RA factors such as life stress, pain and cumulative damage on patient assessment

Underestimation of Disease Activity by Physicians


Underestimation of Disease Activity in a Second Study


- Only 37% of the time did physician judgment agree in patients with moderate disease activity based on DAS28
- Only 68% of the time did physician judgment agree in patients with high disease activity based on DAS28
Challenges with Current Disease Activity Measurements

Acute Phase Reactants as Single Biomarkers (CRP & ESR)

| 2 Observational Studies – Patients with Active RA |
| 1980-2004: Jyväskylä Central Hospital, Finland & Vanderbilt University, TN |
| Normal CRP | Normal ESR | Normal CRP & ESR |
| Finland | Vanderbilt | Finland | Vanderbilt | Finland | Vanderbilt |
| 44% | 58% | 45% | 47% | 33% | 42% |

Golimumab Clinical Trials

<table>
<thead>
<tr>
<th>Patients with 1-4 SJC</th>
<th>Patients with &gt; 4 SJC</th>
</tr>
</thead>
<tbody>
<tr>
<td>50.7% normal CRP &amp; ESR</td>
<td>29.4% normal CRP &amp; ESR</td>
</tr>
</tbody>
</table>

- CRP has shown variation due to genetic expression unrelated to actual disease activity in some RA patients.

Challenges with Composite RA Disease Activity Measurements

DAS28
- 30% of patients in DAS28 remission have 1 or more swollen joints
- Patients can have ≥10 SJC in DAS28 defined remission
- Joint counts are operator skill dependent with high inter- and intra-assessor variability and are poorly reproducible
- Affected by the weather, time of day and comitant diseases

CDAI and SDAI also rely on Joint counts, giving them many of the same limitations mentioned for DAS28

RAPID
- relies only on Patient Reported Outcomes
- Physical Function is not confined to current RA disease activity. Also affected by disease duration and degree of joint damage, both of which can result in irreversible disability.
- Correlation of the RAPID3 to DAS28 can vary widely:
  - 0.36 to 0.61 and average of 0.43

Theodore Pincus; Advantages and Limitations of Quantitative Measures to Assess RA Joint Counts, Radiographs, Laboratory Tests, and Patient Questionnaires; Bulletin of the NYU Hospital for Joint Diseases 2006 (64) 1 & 2: 323-30
Additional Reasons Why Most Doctors Don’t Measure RA Disease Activity Routinely

• “It takes time”
• “Insurance companies will use the information against me”
• Value of the information not clear
  – “That’s for research”
  – “If several joints are swollen, I already know what to do. Why measure the rest?”
  – “Symptoms are most important in how I treat the patient”
• “Where’s the data that this helps?”
• “These measurements doesn’t ‘work’ for some patients”

Discordances between different RA disease activity assessments are well documented

• Acute phase reactants can be normal despite the presence of signs & symptoms1
  – CRP is normal (<1mg/dl) in up to 50% of patients with active RA2,3
  – Only 50% of patients with hsCRP <2mg/L met the ACR criteria of remission in a study of 146 patients4
  – Genetic phenotypes can determine high or low CPR levels independent of RA disease activity5
  – ESR is considered highly unreliable in RA6
  – Not always reflective of underlying disease activity

• Patients without clinical symptoms may still progress radiographically7
  – 19% of patients in physician-defined clinical remission had radiographic progression over 12 months in a study of 102 patients.

Components of RA Composite Indices

<table>
<thead>
<tr>
<th></th>
<th>TJC</th>
<th>SJC</th>
<th>Phys</th>
<th>ESR/CRP</th>
<th>Pt Pain</th>
<th>Pt Global</th>
<th>Phys Fn</th>
</tr>
</thead>
<tbody>
<tr>
<td>DAS28 (0-10)</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>SDAI (0-86)</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>CDAI (0-76)</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>ACR20/50/70</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>HAQ (0-3)</td>
<td></td>
<td></td>
<td>✓</td>
<td>✓</td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>RAPID3 (0-30)</td>
<td></td>
<td></td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
</tbody>
</table>

Modified total Sharp score (mTSS): Measures change in structural damage

How do we measure ‘severe’ RA?? (disease activity, disability, damage)

Disease States Classifications of Composite Indices

<table>
<thead>
<tr>
<th></th>
<th>DAS28ESR</th>
<th>CDAI</th>
<th>SDAI</th>
<th>RAPID3</th>
</tr>
</thead>
<tbody>
<tr>
<td>High disease activity (HDA)</td>
<td>&gt;5.1</td>
<td>&gt;22</td>
<td>&gt;26</td>
<td>&gt;12</td>
</tr>
<tr>
<td>Mod. disease activity (MDA)</td>
<td>3.21 - 5.1</td>
<td>10.1 - 22</td>
<td>11 – 26</td>
<td>6.1 - 12</td>
</tr>
<tr>
<td>Low disease activity (LDA)</td>
<td>2.6 - 3.2</td>
<td>2.8 - 10</td>
<td>11 – 3.3</td>
<td>3.1 - 6</td>
</tr>
<tr>
<td>“Clinical Remission”</td>
<td>≤2.6</td>
<td>≤2.8</td>
<td>≤3.3</td>
<td>≤3.0</td>
</tr>
</tbody>
</table>

PRACTICE VARIABILITY IN RHEUMATOID ARTHRITIS

Frequency of Anti-TNF Use Among US Rheumatologists

- Wide variation in use of anti-TNF agents

Q: How often do you use TNF inhibitors in RA?
Suboptimal Use of DMARDs in RA Patients

- ACR quality measures recommend all RA patients be on a DMARD
- Medical and Pharmacy Claims Prudential Employees and Dependents
- ≥ 18 and ICD-9 code for RA
- 2007 and 2008
- Fully compliant ≥ 270 days DMARD supply or ≥ 12 office procedures for DMARD administration
- Partially compliant 1-269 days DMARD supply or 1-11 office procedures for DMARD administration
- Non-compliant 0 days DMARD supply and 0 office procedures for DMARD administration

DMARD Use in Medicare Managed Care Plans

- Increased from 59% in 2005 to 67% in 2008
- Variability in subsets:
  - Age – 30% less in patients >85 vs. 65-69
  - Mid Atlantic - 7% less and South Atlantic 11% less vs. Pacific region
- Factors associated with being less likely to receive a DMARD
  - Men – 3% less
  - Black race - 4% less
  - Lowest income - 6% less
  - Lowest socioeconomic status - 4% less
  - For profit health plan - 4% less
- DMARD use by plan varied from 16% to 87%
We need information about real world outcomes for specific patient types and risk-benefit information relevant at a patient level. Where do we get this real-world data from?

*Adapted From: Marc C. Levesque, MD, PhD; S. Louis Bridges Jr., MD, PhD; Daniel E. Furst, MD; Philip J. Mease, MD; Overview of Personalized Medicine in Rheumatology. Epocrates online. Duke CME 04-Jan-12
Why Personalized Medicine for RA?

• Relatively common (0.1% - 1% in population)\(^1\)
• Often manifests at early age, reduced mortality and chronicity results in large societal impact\(^1,2\)
• Complexity of treatment
• Cost and risk of adverse effects of current DMARDs “makes it imperative that we identify those individuals most likely to benefit from each therapy”\(^3\)
• Need validated methods to measure and track disease activity


Marc C. Levesque, MD, PhD; S. Louis Bridges Jr., MD, PhD; Daniel E. Furst, MD; Philip J. Mease, MD: Overview of Personalized Medicine in Rheumatology. Epocrates online Duke CME 04 Jan-12

Why Personalized Medicine for RA?

• Waxing/waning disease. Can we identify patients in remission who could stop-treatment while still maintaining remission?\(^1\)
• Strongly immunologic disease: immunologic markers can be tracked for diagnosis and treatment response
• Need validated methods to measure and track disease activity\(^2\)
• RA tends to affect a single system at a time, enabling focus on specific issues for individual patients
• Heterogeneous disease


Marc C. Levesque, MD, PhD; S. Louis Bridges Jr., MD, PhD; Daniel E. Furst, MD; Philip J. Mease, MD: Overview of Personalized Medicine in Rheumatology. Epocrates online Duke CME 04 Jan-12
Regular Quantitative Assessment of RA Is Important to Improve Patient Outcomes

SUPPLEMENT
Tight control in the treatment of rheumatoid arthritis: efficacy and feasibility
M F Bakker, J W G Jacobs, S M M Versteegen, J W J Bijnvo

Effect of a treatment strategy of tight control for rheumatoid arthritis (the TICORA study): a single-blind randomised controlled trial

PCORI Background and Mission

PCORI Mission
The Patient-Centered Outcomes Research Institute helps people make informed health care decisions – and improves health care delivery and outcomes – by producing and promoting high integrity, evidence-based information – that comes from research guided by patients, caregivers and the broader health care community

- PCORI was created by the Patient Protection and Affordable Care Act of 2010 as a non-profit, non-governmental organization
- PCORI’s purpose as defined by the law is to help patients, clinicians, purchasers, and policy makers make better informed health decisions by “advancing the quality and relevance of evidence about how to prevent, diagnose, treat, monitor and manage diseases, disorders, and other health conditions.”
- PCORI will produce knowledge by supporting new research and the analysis and synthesis of existing research
- The statutory language defining PCORI authorizes research that supports a strong “patient-centered” orientation
PCORI Resources

- Funded through the PCOR Trust Fund authorized by Congress as part of the Patient Protection and Affordable Care Act of 2010

FY 2010 - 2012
- $210 million from the Patient-Centered Outcomes Research Trust Fund

FY 2013
- $150 million from the Patient-Centered Outcomes Research Trust Fund
- $1 fee per Medicare and private health insurance beneficiary
- Estimated at $325 million

FY 2014 - 2019
- $150 million from the Patient-Centered Outcomes Research Trust Fund
- $2 fee per Medicare and private health insurance beneficiary
- Estimated at $650 million annually

PCORI vs. NIH R01: Science

<table>
<thead>
<tr>
<th>PCORI R01</th>
<th>NIH R01</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient oriented, patient-relevant</td>
<td>Mechanism-driven</td>
</tr>
</tbody>
</table>

Assessment criteria*
- Impact of condition on health of individuals and populations
- Potential of study to improve health care and outcomes
- Technical merit
- Patient-centeredness
- Patient and stakeholder engagement

Traditional NIH assessment criteria

Stakeholder involvement description in proposal as well as in developing the research question: research team
- Don't necessarily need a patient on your team

Emphasis on patient involvement through out the application
- Emphasis on mechanism and methods

Must follow PCORI Methodology Standards
- No specific methods requirements

* Can vary based on PFA
What is Patient Centered Outcomes Research?

Helps people and their caregivers communicate and make informed health care decisions, allowing their voices to be heard in assessing the value of health care options.

Answers patient-centered questions such as:
1. “Given my personal characteristics, conditions and preferences, what should I expect will happen to me?”
2. “What are my options and what are the potential benefits and harms of those options?”
3. “What can I do to improve the outcomes that are most important to me?”
4. “How can clinicians and the care delivery systems they work in help me make the best decisions about my health and healthcare?”
To answer these questions, PCORI:

- Assesses benefits and harms of preventive, diagnostic, therapeutic, palliative, or health delivery system interventions to inform decision making, highlighting comparisons and outcomes that matter to people;
- Is inclusive of an individual’s preferences, autonomy and needs, focusing on outcomes that people notice and care about such as survival, function, symptoms, and health related quality of life;
- Incorporates a wide variety of settings and diversity of participants to address individual differences and barriers to implementation and dissemination; and
- Investigates (or may investigate) optimizing outcomes while addressing burden to individuals, availability of services, technology, and personnel, and other stakeholder perspectives.
Multiple Networks Sharing Infrastructure

Building a Patient-Powered Research Network (PPRN) for Inflammatory Arthritis
CreakyJoints Patient Network

- Founded 1999 by Seth Ginsberg, founder & arthritis patient
- Active social media engagement with blogs, newsletters, Twitter
- Facebook page very active (most popular arthritis community in world)
- Member registry is pool for PPRN recruitment
- PCORI resources will help build tools to allow patients to self-monitor

Arthritis Patient Partnership with Comparative Effectiveness Researchers (AR-PoWER)

Next-Generation Data for Comparative Effectiveness, Quality of Care, Disease Management

- In-office data collection
- Administrative claims data from health plans
- EHR
- Personal Health Record (PHR)
- At-home PRO data
ACR, EULAR guidelines and PQRS recommend regular assessment

2012 Update of the 2008 American College of Rheumatology Recommendations for the Use of Disease-Modifying Antirheumatic Drugs and Biologic Agents in the Treatment of Rheumatoid Arthritis


Case for a Multi-biomarker Assay for RA Disease Activity

- Current monitoring measures used in clinical practice:
  - subjective evaluation of signs and symptoms
  - limited by assessor variability
  - may not reflect true biological change in a timely manner

- The pathophysiology driving RA inflammation is complex and heterogeneous.
  - CRP and ESR cannot capture the full complement of RA-specific disease process

- The simultaneous use of multiple biomarkers in a single test algorithm may provide a more comprehensive quantitative representation of the overall complex heterogeneous biology of RA


Developed this slide based on Dr. Mease’s publication on Vectra DA / biomarkers for RA. Probably want to ask permission to use this one.
Could Biomarkers Help Manage RA?

- Objectively track improvement in response to therapy
- Support tight control management of RA
- Assist in clinical management if more information related to assessment is needed
- Proxy for synovitis on MSK US & MRI
- Allow for more rapid switching of therapies in clinical practice, and in Phase 2-3 research studies
- Improve patient-physician communication
- Predict
  - Radiographic progression
  - Flare; need to re-dose RTX
  - Successful therapy withdrawal

Multi-biomarker Approaches May Better Capture the Biological Complexity of RA and Complement Clinical Assessment

- Complex diseases involving multiple biological pathways are less likely to be captured by single biomarkers
- Multi-biomarker approaches can integrate information from diverse pathways into a single quantitative score for simple interpretation
A Multi-Biomarker Assay for Measuring RA Disease Activity: A Multi-step Development Process

**Biomarker Screening**
- Identify candidate biomarkers

**Feasibility**
- >500 patients
- >700 samples
- Qualify assays
- Select top biomarkers
- Build prototypes
- Prepare for development

**Development**
- >700 patients
- >800 samples
- Optimize analytical performance of individual assays
- Develop algorithm
- Verify algorithm
- Validate analytically

**Validation**
- >400 patients
- >400 samples
- Evaluate final algorithm in independent cohort

396 Candidate Biomarkers
130 Candidate Biomarkers*
25 Candidate Biomarkers
12 Final Biomarkers

Validated MBDA

* 130 biomarkers were assayed in feasibility studies of disease activity; additional biomarkers were assessed only for technical feasibility

---

Multibiomarker Disease Activity Test: A Multi-step Development Process

**Biomarker Screening**
- Identify candidate biomarkers

**Feasibility**
- >500 patients
- >700 samples
- Qualify assays
- Select top biomarkers
- Build prototypes
- Prepare for development

**Development**
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- Develop algorithm
- Verify algorithm
- Validate analytically

**Validation**
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12 Final Biomarkers

Validated MBDA

* 130 biomarkers were assayed in feasibility studies of disease activity; additional biomarkers were assessed only for technical feasibility

Adapted from: Bakker et al. Presented at: ACR 2010; Poster #1753
### Biomarkers: Categories and Primary Role

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Biomarker Category</th>
<th>Primary Role</th>
</tr>
</thead>
<tbody>
<tr>
<td>VCAM-1</td>
<td>Adhesion Molecules</td>
<td>Cellular influx and tissue expansion</td>
</tr>
<tr>
<td>EGF</td>
<td>Growth Factors</td>
<td></td>
</tr>
<tr>
<td>VEGF-A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IL-6</td>
<td>Cytokine-related Proteins</td>
<td>Local inflammation and destruction</td>
</tr>
<tr>
<td>TNF-RI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MMP-1</td>
<td>Matrix Metalloproteinases</td>
<td>Cartilage degradation and joint damage</td>
</tr>
<tr>
<td>MMP-3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>YKL-40</td>
<td>Skeletal-related Proteins</td>
<td>Stromal activity &amp; regulation (fibroblasts, chondrocytes, vascular cells)</td>
</tr>
<tr>
<td>Leptin</td>
<td>Hormones</td>
<td>Systemic Inflammatory Response</td>
</tr>
<tr>
<td>Resistin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SAA</td>
<td>Acute Phase Proteins</td>
<td></td>
</tr>
<tr>
<td>CRP</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### RA: A Disease with a Diverse Biology

[Diagram depicting the diverse biology of RA with various biomarkers and their effects on different cell types and tissue degradation.]
Multi-Biomarker Test Validation and Performance

- The Vectra DA score was significantly associated with disease activity categories compared to the gold standard of the DAS28CRP* (p<0.001)

  RF+ and/or Anti-CCP+
  - AUROC = 0.77*

  RF- and Anti-CCP-
  - AUROC = 0.70*

---

Multi-biomarker Test Validation and Performance

- MBDA score significantly associated with disease activity categories compared to gold standard, DAS28CRP* (p<0.001)¹

- MBDA score significantly correlated with several composite disease activity measures, including DAS28ESR, CDAI, and SDAI (p<0.001 for each), both cross-sectionally and longitudinally²,³

- MBDA score significantly correlated with patient-reported outcomes, including HAQ, ΔHAQ, and RAPID3 (p<0.001 for HAQ and ΔHAQ; p<0.003 for RAPID3)¹,³

- MBDA score significantly correlated with future x-ray damage 1-2 years later ⁴

---

MBDA = multi-biomarker disease activity test
*low versus moderate/high disease activity using DAS28CRP = 2.67 as the threshold

¹Curtis et al. Arthritis Care & Research 2012; 64(12):1794-1803
⁴van der Helm-van Mil, et al. A&R 2011 63(suppl 10): 121
**Multi-Biomarker Disease Activity Test Quickly Identified Patients Who Will Respond to Treatment**

![Graph showing change in Vectra DA score over weeks for RA + FM and RA alone groups.](Arthritis Care Res (Hoboken). 2012 Dec;64(12):1794-803)

---

**Vectra® DA scores were similar in RA patients with or without fibromyalgia**

- DAS28-CRP and Patient Global Assessment were statistically significantly different between the RA + FM and RA alone groups

<table>
<thead>
<tr>
<th>Measure</th>
<th>RA + FM (N=25)</th>
<th>RA alone (N=173)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vectra DA</td>
<td>33</td>
<td>32</td>
<td>0.65</td>
</tr>
<tr>
<td>DAS28-CRP</td>
<td>3.59</td>
<td>2.80</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Patient global assessment*</td>
<td>50</td>
<td>15</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TJC</td>
<td>6.6</td>
<td>4.0</td>
<td>0.06</td>
</tr>
<tr>
<td>SJC</td>
<td>3.8</td>
<td>2.5</td>
<td>0.32</td>
</tr>
<tr>
<td>CRP mg/dL*</td>
<td>0.2</td>
<td>0.16</td>
<td>0.83</td>
</tr>
</tbody>
</table>

*Values are means except for patient global assessment and CRP, which are medians. P-values were by t-test, except for patient global assessment and CRP, which were by Wilcoxon rank-sum test.

---

Lee, YC, et al. EULAR 2013, poster # SAT0099
Frequency of radiographic progression was markedly greater when MBDA score was high, even when CRP was low.

Baseline CRP mg/dL

- Low (≤1)
- Moderate (1−3)
- High (>3)

Frequency (%) of Progression (ΔSHS > 3 in a 12 month period)

<table>
<thead>
<tr>
<th>Baseline Vectra DA Alg Score</th>
<th>N=271 visits, 163 patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>9%</td>
</tr>
<tr>
<td>Moderate</td>
<td>21%</td>
</tr>
<tr>
<td>High</td>
<td>50%</td>
</tr>
<tr>
<td>NP</td>
<td>50%</td>
</tr>
<tr>
<td>NP</td>
<td>50%</td>
</tr>
</tbody>
</table>

MBDA = multi-biomarker of disease activity
Li W, et al, EULAR 2013, poster # FRI0098; NP = No Patients.

Rapid radiographic progression at 1 year in patients with high MBDA score (>44) was observed across CRP categories at baseline.

Rapid Radiographic Progression (ΔSHS > 5) at 1 year

- Low (≤30)
- Moderate (30−44)
- High (>44)
- ΔSHS >5 (n = 43)

<table>
<thead>
<tr>
<th>Baseline Vectra DA</th>
<th>n=71</th>
<th>n=75</th>
<th>n=89</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>5</td>
<td>24</td>
<td>10</td>
</tr>
<tr>
<td>Moderate</td>
<td>0</td>
<td>4</td>
<td>11</td>
</tr>
<tr>
<td>High</td>
<td>1</td>
<td>88</td>
<td>21</td>
</tr>
</tbody>
</table>
High Biomarker Score in patients in DAS28CRP remission indicates increased joint damage risk

The Vectra DA algorithm and biomarkers were used in a study performed in Crescendo’s R&D lab.

Risk of radiographic progression for patients in DAS28CRP remission

Risk of Progression

Δ TSS Threshold for Progression

- RR=1.5: 87%
- RR=2.3: 47%
- RR=3.1: 33%

* p<0.05

EAC = Early Arthritis Cohort; TSS = total van der Heijde sharp score; DAS CRP remission=(< 2.32); High Vectra DA algorithm score=(> 44)

van der Helm-van Mil, et al. A&R 2011 63(suppl 10): 121

38% of treatment plans changed after HCPs saw Vectra DA score (N=101)

<table>
<thead>
<tr>
<th>Type of Change</th>
<th>Patients with a Treatment Change (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in drug (addition, discontinuation, switch)</td>
<td>21</td>
</tr>
<tr>
<td>Change in dosing or frequency (increase or decrease)</td>
<td>10</td>
</tr>
<tr>
<td>Change in route of administration (injection or oral)</td>
<td>3</td>
</tr>
<tr>
<td>Combination change in dosing, frequency, route administration</td>
<td>4</td>
</tr>
<tr>
<td><strong>Total changes</strong></td>
<td><strong>38</strong></td>
</tr>
</tbody>
</table>

95% CI = 29% - 47%

Types of Drug Changes Triggered By Use of Multi-Biomarker test (n=101 patients)

<table>
<thead>
<tr>
<th>Type of Change</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any change in treatment regimen (drug, dose, frequency, route of administration)</td>
<td>38</td>
</tr>
<tr>
<td>Escalation of care</td>
<td></td>
</tr>
<tr>
<td>Drug additions¹</td>
<td>21</td>
</tr>
<tr>
<td>De-escalation of care</td>
<td></td>
</tr>
<tr>
<td>Drug removals²</td>
<td>10</td>
</tr>
<tr>
<td>Drug switches³</td>
<td></td>
</tr>
</tbody>
</table>

¹Addition means addition of a biologic or a conventional DMARD
²Removal means removal of a biologic or a conventional DMARD
³Switch means switch from one biologic to another biologic or one conventional DMARD


High Biomarker Score in patients in DAS28CRP remission indicates increased joint damage risk

![Graph showing risk of radiographic progression for patients in DAS28CRP remission](image)

- RR=1.5* 87%
- RR=2.3* 47%
- RR=3.1* 33%

EAC = Early Arthritis Cohort; TSS = total van der Heijde sharp score; DAS CRP remission=[< 2.3]; High Vectra DA algorithm score=[> 44]


The Vectra DA algorithm and biomarkers were used in a study performed in Crescendo’s R&D lab.
CLINICAL APPLICATIONS OF A MULTI-BIOMARKER DISEASE ACTIVITY TEST

APPLICATIONS OF ASSESSING RA DISEASE ACTIVITY:

Tracking changes in disease activity in response to change in therapy
APPLICATIONS OF ASSESSING RA DISEASE ACTIVITY:

Low Disease Activity and Remission

Significant Correlation with Imaging Modalities

• Radiographic Progression
• MRI Synovitis and Osteitis
Addressing clinical challenges

• CRP
• Comorbidities

PUTTING IT ALL TOGETHER:
A CASE STUDY
**Background**

- 75 year old female w/ osteoarthritis presented to her PCP with pain, swelling, and stiffness
- Diagnosed with seronegative (RF-, anti-CCP-) RA, administered cortisone injections in her hands and referred her to a rheumatology practice
- X-ray of left and right hand showed mild JSN of interphalangeal joints
- Vectra DA ordered as part of baseline assessment of disease activity

### Disease Activity Measurements

- SJC(66) = 11
- TJC(68) = 13

### Labs

- CRP* = 94 mg/L
- ESR = 57 mm/hr

---

**High Vectra DA Score Consistent with Other Disease Activity Measures**

### Disease Activity Measurements

- SJC(66) = 11
- TJC(68) = 13

### Labs

- CRP* = 94 mg/L
- ESR = 57 mm/hr
- MBDA score = 75 (high disease activity)

**Management Plan:**

- Methotrexate (starting at 7.5 mg/wk SQ and increasing to 20 mg/wk SQ) and prednisone (starting at 5 mg/day and increasing to 10 mg/day).
- At the end of November, patient refused adding a biologic to her regimen. Hydroxychloroquine was added.

---

*CRP levels reported are from Vectra DA.
Based on information from an actual patient case; actual MBDA scores; individual identifiers including actual dates of service have been modified to protect patient privacy.
### Disease Activity Appears to have Declined and then Stabilizes

#### March – August 2011

<table>
<thead>
<tr>
<th>Follow-up visits</th>
<th>Disease Activity Measurements 3/11</th>
</tr>
</thead>
</table>
| • March 2011: marked clinical improvement | • SJC(66) = 0  
• August 2011: disease activity appeared stable.  
  • The TJC was 8, however the tender joints were the CMC joints and PIP joints, which is frequently seen in OA, less than RA.  
• TJC(68) = 0  
• ESR = 3 mm/hr  
• MBDA Score = 34 |

**Action Taken**

• March 2011: Meloxicam was added to help with joint pain and stiffness, believed to be related to OA.

---

### At Routine Follow-up Visit, Patient Appears To Be Doing Well

#### January 11, 2012

<table>
<thead>
<tr>
<th>Follow-up visit</th>
<th>Disease Activity Measurements</th>
</tr>
</thead>
</table>
| • Patient had minor hand and wrist pain, 0 swollen and 2 tender joints | • SJC(66) = 0  
• TJC(68) = 2  
• ESR = 2 mm/hr |

**Action Taken**

• Ordered MBDA to capture an assessment prior to making any changes, and the sample was taken that day.
• Reduced the current dose of prednisone (8mg/weekly) by 1 mg every two weeks.

*Based on information from an actual patient case; actual MBDA scores; individual identifiers including actual dates of service have been modified to protect patient privacy.*
MBDA Score is 53, Indicating High Disease Activity

Based on information from an actual patient case; actual MBDA scores; individual identifiers including actual dates of service have been modified to protect patient privacy.

Follow-up visit

• ~2 weeks later, the patient called to make an appointment because she was not feeling well.

• Patient came in for the visit complaining of bilateral shoulder pain and hand pain that had been severe for several days.

• SJC and TJC were both 23

• The rheumatologist noted that the high MBDA score had preceded the symptoms.

Elevated MBDA Score Preceded Clinical Symptoms

January 30, 2012

Disease Activity Measurements

• SJC(66) = 23
• TJC(68) = 23
Abatacept is Added to Management Plan

- Abatacept was started in February
- MBDA Score was 35 (moderate disease activity) in April and 26 (low disease activity) in July

* No MBDA taken at the Jan 30, 2012 visit; δ CRP levels reported are from MBDA
Based on information from an actual patient case; actual MBDA scores; individual identifiers including actual dates of service have been modified to protect patient privacy.

MBDA assists with achieving disease control in a patient reluctant to treat their RA
Case Study: newly diagnosed RA patient, referred by naturopathic physician

**Background**
- 72 year old female referred by naturopathic physician with symptoms of RA
- Very difficult to convince to take medication
  - patient intent on only using naturopathic medicines

**May 2012 Visit**
- Diagnosed with seronegative (RF- and Anti-CCP-) RA by rheumatologist
  - Symmetric Polyarthritis > 6 wks
  - Visible swelling of joints of the hand
  - No recent illness
  - Elevated ESR
- Current RA Medications: prednisone 10 mg qd
- Other Medications: turmeric, bromelin, evening primrose, cod liver oil
- MBDA ordered as a baseline measure of disease activity

**MBDA supports physician assessment of disease activity**

**May 2012 Visit (Continued)**

**Disease Activity Measurements**
- SJC(28): 7
- TJC(28): 5
- Patient Global: 2 (0-10 scale)
- Pain VAS: 2 (0-10 scale)
- RAPID3: 3.3/10 (Moderate)

- CDAI: 14.3 (Moderate)
- CRP: 0.7 mg/dL (from MBDA report)

**MBDA Score and Management Plan**

<table>
<thead>
<tr>
<th>MBDA Score =</th>
<th>Management Plan:</th>
</tr>
</thead>
<tbody>
<tr>
<td>55</td>
<td>• Patient is started on MTX 15 mg QW</td>
</tr>
<tr>
<td></td>
<td>• Prednisone self-tapered to zero by August 1</td>
</tr>
</tbody>
</table>

Based on information from an actual patient case; actual MBDA scores; individual identifiers including actual dates of service have been modified to protect patient privacy.
Patient has active disease and is reluctant to take a biologic

Follow-up visit
- Patient returns for a follow-up visit and continues to express reluctance to treat her RA with medication

<table>
<thead>
<tr>
<th>Disease Activity</th>
<th>Current Medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>SJC: 5</td>
<td>RAPID3: 7/10 (High)</td>
</tr>
<tr>
<td>TJC: 2</td>
<td>CDAI: 13.8 (Mod)</td>
</tr>
<tr>
<td>Patient Global: 3</td>
<td>ESR: 67 mm/hr</td>
</tr>
<tr>
<td>Pain VAS: 3</td>
<td></td>
</tr>
</tbody>
</table>

Action Taken
- MBDA ordered to assist with the patient conversation

Based on information from an actual patient case; actual MBDA scores; individual identifiers including actual dates of service have been modified to protect patient privacy.

MBDA score used to assist with patient conversation regarding starting a biologic

MBDA Score = 71 (High Disease Activity)

Action Taken:
- MTX ↑ to 20mg QW; Prednisone added back at 5 mg
- Patient scheduled to come in next month to be seen due to high disease activity
- Will discuss a biologic w/ patient

Based on information from an actual patient case; actual MBDA scores; individual identifiers including actual dates of service have been modified to protect patient privacy.
September Visit: Planned review of MBDA score, X-Ray and to discuss addition of biologic

September 30, 2012

Disease Activity | Current Medication
--- | ---
SJC(28): 8 | Patient Global: 2
TJC(28): 8 | RAPID3: 4.2/10 (high)
Pain VAS: 1.5 | • MTX 20 mg QW
• Prednisone 5 mg QD

Action Taken
- MBDA score of 71 was reviewed with patient.
- Need for more aggressive treatment with biologic therapy was discussed.
  - Patient continues to refuse biologic therapy
  - Patient revealed that she was not being compliant with her MTX therapy
- Compliance w/ MTX discussed w/ patient and Naturopath
- Hydroxychloroquine 200mg qd added
- MBDA ordered to continue to assist with patient conversation about compliance with current meds and addition of biologic (anti-TNF therapy).

MBDA score is 70, indicating continued high disease activity

October 2012 (MBDA Test Report Received)

Other Results:
- CRP = 2.1 mg/dL

Action Taken:
- MBDA score supports clinical assessment of high disease activity
- MBDA score will be used to assist in discussion with patient about biologic agent at next visit
- Patient being brought back in within the next 4-6 weeks
Clinical disease activity improves, however, remains elevated

November 17th, 2012

**Disease Activity**
- SJC(28): 5
- TJC(28): 6
- Pain VAS: 1.5

**Current Medication**
- Patient Global: 1.5/10
- RAPID3: 3.3/10 (mod)

- MTX 20 mg QW
- HCQ 200 mg QD
- Prednisone 5mg QD

**Action Taken**
- Patient reports improvement, but clinical disease activity has not improved significantly
- MBDA ordered at this visit to assess disease activity to help clarify patient and physician discordance
- Biologic discussed in context of previous MBDA score (70) and patient expresses willingness to try biologic and golimumab 50mg QM is ordered

---

**MBDA score prior to addition of golimumab**

**November 2012**

**MBDA Score = 40 (Moderate Disease Activity)**

**Action Taken:**
- MBDA score showed marked improvement from previous visits, clinical exam only a bit better
- MD decides to not initiate anti-TNF therapy at this point

Based on information from an actual patient case; actual MBDA scores; individual identifiers including actual dates of service have been modified to protect patient privacy.
**Patient demonstrates improvement, golimumab was not started**

**January 20th, 2013**

### Disease Activity / Laboratory Values

- **SJC(28):** 2
- **TJC(28):** 1
- **Pain VAS:** 0.5
- **Patient Global:** 0.5
- **RAPID3:** 1/10 (near remission)

### Current Medication

- MTX 20 mg QW
- HCQ 200 mg QD
- Prednisone 5mg QD

### Action Taken

- MD and patient happy with response of MTX, Prednisone and HCQ
- Patient understands the need for compliance
- Biologic not necessary
- Plan to recheck MBDA and clinical disease activity in 3 mos to evaluate for remission

---

**Conclusion**

- MBDA was used to assist with achieving disease control in an RA patient who is highly resistant to treatment beyond naturopathic medicines.
  - Assisted with patient conversations about initiating RA medications.
  - Helped to demonstrate to the patient the importance of compliance and the impact of medication compliance on the activity of the disease.
  - Drop in MBDA score in November reflected more of an improvement biologically than by clinical exam and informed medication plan.
  - Assisted with decision to maintain patient on DMARDs only.
Conclusion of Case Study

- MBDA used to assist with achieving disease control in an RA patient who is highly resistant to treatment beyond naturopathic medicines
  - Assisted with patient conversations about initiating RA medications
  - Helped demonstrate to the patient the importance of compliance
  - Drop in MBDA score in November reflected more of an improvement biologically than by clinical exam and informed medication plan.

- Assisted with decision to maintain patient on DMARDs and not use biologics

Based on information from an actual patient case; actual MBDA scores; individual identifiers including actual dates of service have been modified to protect patient privacy.

Conclusion

- The MBDA helped to:
  - assess RA disease activity in a patient with a confounding comorbidity of osteoarthritis in the hands
  - establish a baseline measure of RA disease activity
  - to track changes in RA disease activity in response to treatment changes (both DMARDs and a biologic agent)
  - engage in a conversation with the patient to support initiation of a biologic agent

- A high MBDA score was observed prior to an increase in clinical symptoms of RA disease activity.

Based on information from an actual patient case; actual MBDA scores; individual identifiers including actual dates of service have been modified to protect patient privacy.
ADDITIONAL USES OF BIOMARKERS IN RA

Potential to Meet Multiple Unmet Clinical Needs

- EARLY Dx
- DIFFERENTIAL Dx
- SUB-TYPING
- PROGNOSIS
- STRUCTURAL DAMAGE (SD)
- DISEASE ACTIVITY (DA)
- CARDIOVASCULAR RISK
- ANTI-DRUG ANTIBODY
- NON-TNF CLASS RX RESPONSE
- TNF CLASS RX RESPONSE
- DMARD Rx DOSE/RESPONSE
Opportunity to span entire disease process over years

Potential Products
1. Diagnosis
2. Sub‐typing
3. Disease Activity
4. Prognosis
5. Structural Damage
6. DMARD Dosing
7. Biologics Rx Selection
8. Cardiovascular Risk

Advantages:
- Integrate findings, track patient progress
- Leverage same patient – multiple tests
- High switching costs and barriers

Overall Summary
- RA causes progressive joint damage, functional impairment disability, and economic hardship
- Clinical assessment of RA remains subjective and imprecise, despite evidence that elimination of joint inflammation (i.e. remission) is needed for the best possible outcomes.
- Rheumatologists, patients and payers can benefit from more quantitative disease activity measurement in RA
- As a complement to clinical assessment, a multi‐biomarker test that enables accurate assessment of disease activity can facilitate more rapid and rational treatment decisions
- Need better data on who does NOT need life‐long biologic therapy, no good predictors at present
- Major investment from PCORI has recently created new infrastructure for comparative effectiveness research; exciting opportunities for participation by health plans and health systems to partner together and with patients
Median changes in Vectra® DA Scores corresponded with EULAR response levels in MTX-treated patients at month 3

EULAR Responder Level at 3 Months

-3 (-5%)  
-14 (-25%)  
-18 (-30%)

None  
Moderate  
Good

(n=71)  
(n=107)  
(n=101)

* P value is < 0.0001 between non responder and moderate or non responder and Good
Median Baseline Vectra DA Score = 59
Crescendo Bioscience Data on file

Median changes in Vectra® DA Alg Score differed significantly between EULAR Response categories in anti-TNF§-treated patients at week 52

EULAR Responder Level at Week 52

+2 (+4%)  
-21 (-35%)  
-29 (-50%)

Non-Responder  
Moderate Responder  
Good Responder

(n=12)  
(n=52)  
(n=83)

§ adalimumab, etanercept, infliximab
Median Baseline Vectra DA Algorithm score = 64
Hirata, S. et al., A&R 2012;64(suppl 10):S1130 and Crescendo Bioscience data on file
The Vectra DA algorithm and biomarkers were used in a study performed in Crescendo’s R&D lab
Rapid radiographic progression at 1 year in patients with high Vectra® DA (>44) was observed across CRP categories at baseline.

---

**Baseline CRP (mg/dL)**

<table>
<thead>
<tr>
<th>CRP Category</th>
<th>n</th>
<th>Number of Patients with Rapid Radiographic Progression (ΔSHS &gt; 5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low (≤1)</td>
<td>71</td>
<td>5</td>
</tr>
<tr>
<td>Mod (1–3)</td>
<td>75</td>
<td>26</td>
</tr>
<tr>
<td>High (&gt;3)</td>
<td>89</td>
<td>42, 10, 41, 11, 5</td>
</tr>
</tbody>
</table>

---

Frequency of radiographic progression was markedly greater when Vectra® DA algorithm score was high, even when CRP was low.

---

**Baseline CRP mg/dL**

<table>
<thead>
<tr>
<th>CRP Category</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low (≤1)</td>
<td>21%</td>
</tr>
<tr>
<td>Mod (1–3)</td>
<td>5%</td>
</tr>
<tr>
<td>High (&gt;3)</td>
<td>50%</td>
</tr>
</tbody>
</table>

**Baseline Vectra DA Alg Score**

- Low
- Moderate
- High

N = 271 visits, 163 patients
Vectra® DA scores were similar in RA patients with or without fibromyalgia

- DAS28-CRP and Patient Global Assessment were statistically significantly different between the RA + FM and RA alone groups.

<table>
<thead>
<tr>
<th></th>
<th>RA + FM (N=25)</th>
<th>RA alone (N=173)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vectra DA</td>
<td>33</td>
<td>32</td>
<td>0.65</td>
</tr>
<tr>
<td>DAS28-CRP</td>
<td>3.59</td>
<td>2.80</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Patient global assessment*</td>
<td>50</td>
<td>15</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TJC</td>
<td>6.6</td>
<td>4.0</td>
<td>0.06</td>
</tr>
<tr>
<td>SJC</td>
<td>3.8</td>
<td>2.5</td>
<td>0.32</td>
</tr>
<tr>
<td>CRP mg/dL*</td>
<td>0.2</td>
<td>0.16</td>
<td>0.83</td>
</tr>
</tbody>
</table>

*Values are means except for patient global assessment and CRP, which are medians. P-values were by t-test, except for patient global assessment and CRP, which were by Wilcoxon rank-sum test.

Lee, YC, et al. EULAR 2013, poster #SAT0099

Median changes in Vectra® DA Scores corresponded with EULAR response levels in MTX-treated patients at month 3

Mann Whitney U test

-3 (-5%) P < 0.0001*
-14 (-25%) P < 0.0001*
-18 (-30%) P < 0.0001*

Median Baseline Vectra DA Score = 56
Crescendo Bioscience Data

* P value < 0.0001 between non responder and moderate or non responder and good

EULAR Responder Level at 3 Months

Crescendo Bioscience Data
Median changes in Vectra® DA Alg Score differed significantly between EULAR Response categories in anti-TNF §-treated patients at week 52.

Median Baseline Vectra DA algorithm score = 64

The Vectra® DA algorithm and biomarkers were used in a study performed in Crescendo’s R&D lab.


Anti-TNF / UOEH