OPTIMIZING THE TREATMENT OF RHEUMATOID ARTHRITIS IN 2013

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Outline

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

# Risk Factors for RA

## Risk Factors for Developing RA

<table>
<thead>
<tr>
<th>Non-Modifiable Factors</th>
<th>Modifiable Factors</th>
</tr>
</thead>
<tbody>
<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

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>– Long-standing RA</td>
<td>– High titer RF+, CCP+</td>
</tr>
<tr>
<td>– Rheumatoid nodules</td>
<td>– Antinuclear antibodies</td>
</tr>
</tbody>
</table>

RF=rheumatoid factor; CCP=cyclic citrullinated peptide

## 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

Synovial fluid

Pannus

Major cell type: neutrophils

Cartilage Thinning

Ulnar deviation mcp subluxation
Symmetric Polyarthritis—Swan-Neck Deformity
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
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

- TNFα
- IL-1
- IL-6

Activates

- Proteases and Cytokines
- RF Autoantibodies

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.
Work Disability Associated With RA

Patients ≤64 y no longer employed who attribute this to RA

Widening Mortality Gap in RA

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

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
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

### Annual Indirect Costs\textsuperscript{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\textsuperscript{b}</strong></td>
<td></td>
</tr>
</tbody>
</table>

\textsuperscript{a} Adjusted mean.
\textsuperscript{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.
Higher Disease Activity Associated with Increased Direct Cost

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

* Converted to dollars; $1=0.7 €
Beresniak A et al. J Rheumatol 2011;38:439–45
MANAGEMENT OF RA
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,⁵ JAMES O’DELL,⁶ KEVIN L. WINTHROP,⁷ TIMOTHY BEUKELMAN,¹ S. LOUIS BRIDGES JR.,¹ W. WINN CHATHAM,¹ HAROLD E. PAULUS,² MARIA SUAREZ-ALMAZOR,⁸ CLAIRE BOMBARDIER,⁹ MAXIME DOUGADOS,¹⁰ DINESH KHANNA,¹¹ CHARLES M. KING,¹² AMYE L. LEONG,¹³ ERIC L. MATTESON,¹⁴ JOHN T. SCHOUSBOE,¹⁵ EILEEN MOYNIHAN,¹⁶ KAREN S. KOLBA,¹⁷ ARCHANA JAIN,¹ ELIZABETH R. VOLKMAN,² HARSH AGRAWAL,² SANGMEE BAE,² AMY S. MUDANO,¹ NIVEDITA M. PATKAR,¹ AND KENNETH G. SAAG¹
Management of Established RA from the 2012 ACR Recommendations

Figure 2: Established RA

- **Low Disease Activity without Poor Prognosis**: DMARD monotherapy → Reassess*
  - A. Add MTX, HCQ or LEF (as appropriate) → Reassess*

- **Low Disease Activity with Poor Prognosis** OR Moderate/High Disease Activity:
  - MTX monotherapy or Combination DMARD therapy (including double or triple therapy) → Reassess*
  - B. Add or switch to another DMARD → Reassess*

- **C. Add OR switch to anti-TNF biologic**: Reassess OR if serious adverse event
  - If serious adverse event: Switch to a non-TNF biologic
  - If non-serious adverse event: Switch to anti-TNF biologic OR non-TNF biologic

- **Reassess**: G. Switch to another type or category of anti-TNF or non-TNF biologic
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, Curtis et. al. Arth Rheum 2012
## 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.
MEASUREMENT OF RA
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...
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)
- Laboratory values
  ESR/CRP, RA, ACP/CCP

*Is or contains patient-reported outcome measures.
What We DO Measure

- Scored HAQ: 15.4%
- Patient Global VAS: 34.1%
- Pain VAS: 38.3%
- 28 Joint Count: 38.8%
- DAS: 12.2%
- ESR: 83.9%
- CRP: 77.1%
- CCP: 71.1%

Cush J. presented at the American College of Rheumatology meeting 2008.
**Physician Quality Reporting System (PQRS)**

### Benefit of reporting:
- Initially 2% bonus on Medicare part B revenues
- Now fallen to 0.5%
- 2% penalty starting in 2014

*Curtis et. al., Arthritis Care Res 2013 Feb;65(2):235-43.*

### Measure #2: Periodic Assessment of Disease Activity

<table>
<thead>
<tr>
<th>Measure Description</th>
<th>Technical Specifications: Administrative Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentage of an assessed</td>
<td>Denominator (Eligible Population)</td>
</tr>
<tr>
<td></td>
<td>All patients 16 years and older with a diagnosis of Rheumatoid Arthritis (RA)</td>
</tr>
<tr>
<td></td>
<td>CPT E/M Service Code:</td>
</tr>
<tr>
<td></td>
<td>• 99201, 99202, 99203, 99204, 99205, 99211, 99212, 99213, 99214, 99215, 99241, 99242, 99243, 99244, 99245, 99455, 99456</td>
</tr>
<tr>
<td></td>
<td>AND</td>
</tr>
<tr>
<td></td>
<td>ICD-9 Code for RA:</td>
</tr>
<tr>
<td></td>
<td>• 714.0, 714.1, 714.2, 714.81</td>
</tr>
<tr>
<td>Numerator</td>
<td>Patients with disease activity assessed by a standardized descriptive or numeric scale or composite index and classified into one of the following categories: low, moderate or high, at least once within 12 months</td>
</tr>
<tr>
<td>Denominator</td>
<td>None</td>
</tr>
</tbody>
</table>

Only 10-15% of U.S. rheumatologists reported in 2009
Possibilities Why Most Doctors Don’t Measure RA Disease Activity

- “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”
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

Principles of Tight Control in RA

• Treatment goal is remission
  – 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

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

* Sequential monotherapy and step up combination therapy vs. standard of care (SOC) – initial IFX + MTX arm not included. Included primarily of traditional DMARDs, (tight control had 11% infliximab use during year 1 vs. 2% in SOC)
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
Patient Reported Measures

- 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
Variability in Disease Activity Measures

• 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
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 concomitant 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: 323-39
Summary: Discordance between different RA disease activity assessments are well documented

- Physician and patient assessments are relatively subjective and may differ\(^1\)
  - Joint Assessments
    - TJC$s in context of fibromyalgia, nodal osteoarthritis
    - “Swollen joints” — fibrous thickening vs synovitis
  - Patient Global
    - Frequently includes comorbid symptoms (headache, back pain)
    - Includes nonreversible functional impairment
  - HAQ/MDHAQ (disability)
    - Allows for irreversible disability (floor effect)

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

- **Objectively** track improvement in response to therapy
- Support tight control management of RA
- Assist in clinical management when more information 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 Vectra DA

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

IL-6, TNF-RI
VCAM-1
EGF, VEGF
MMP-1, MMP-3
YKL-40
leptin, resistin
SAA, CRP

systemic inflammatory response

peripheral blood and organs

peripheral

endothelial cells

leukocyte recruitment & angiogenesis

T cells

adaptive immunity

B, plasma cells

monocytes, macrophages, dendritic cells

innate immunity

fibroblast-like synoviocytes

hyperplasia

cartilage

epbone

osteoclasts

osteoblasts

chondrocytes

MMP1 YKL40

MMP3

cartilage degradation

bone erosion

neutrophils

CRP SAA

res

lept

res

res

res

res

res
Multi-Biomarker Test Performance and Validation

- The multi-biomarker score is significantly associated with disease activity categories compared to the gold standard of the DAS28CRP* ($p<0.001$) in validation studies.

new slide may replace this
Jeffrey Curtis, 4/11/2013
High Biomarker Score in patients in DAS28CRP remission indicates increased joint damage risk

Risk of radiographic progression for patients in DAS28CRP remission

- Risk of progression for DAS28CRP Remission (n=83)
  - >0: 58%
  - >3: 47%
  - >5: 33%

- Risk of progression for DAS28CRP Remission and High Vectra DA algorithm score (n=15)
  - >0: 87%
  - >3: 47%
  - >5: 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

The Vectra DA algorithm and biomarkers were used in a study performed in Crescendo’s R&D lab.
## Types of Drug Changes Triggered By Use of Multi-Biomarker test

<table>
<thead>
<tr>
<th>Type of Change</th>
<th>Patients with a Treatment Change (n=101)</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 additions(^1)</td>
<td>21</td>
</tr>
<tr>
<td>De-escalation of care</td>
<td>10</td>
</tr>
<tr>
<td>Drug removals(^2)</td>
<td>10</td>
</tr>
<tr>
<td>Drug switches(^3)</td>
<td>4</td>
</tr>
</tbody>
</table>

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

CASE STUDY
Baseline Assessment in Newly Diagnosed RA Patient

Visit 1: November 2010

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

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

Visit 1: November 2010 (Continued)

<table>
<thead>
<tr>
<th>Disease Activity Measurements</th>
<th>Labs</th>
</tr>
</thead>
<tbody>
<tr>
<td>• SJC(66) = 11</td>
<td>• CRP* = 94 mg/L</td>
</tr>
<tr>
<td>• TJC(68) = 13</td>
<td>• ESR = 57 mm/hr</td>
</tr>
<tr>
<td></td>
<td>• MBDA score = 75 (high disease activity)</td>
</tr>
</tbody>
</table>

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 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.
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>
<tbody>
<tr>
<td>• March 2011: marked clinical improvement</td>
<td>• SJC(66) = 0</td>
</tr>
<tr>
<td>• August 2011: disease activity appeared stable.</td>
<td>• TJC(68) = 0</td>
</tr>
<tr>
<td>• The TJC was 8, however the tender joints were the CMC joints and PIP joints,</td>
<td>• ESR = 3 mm/hr</td>
</tr>
<tr>
<td>which is frequently seen in OA, less than RA.</td>
<td>• <strong>MBDA Score = 34</strong></td>
</tr>
</tbody>
</table>

| Disease Activity Measurements 8/11                                            |
|--------------------------------------------------------------------------------|-------------------------------------------------------------------------|
| • SJC(66) = 0                                                                  | • TJC(68) = 8                                                           |
| • TJC(68) = 8                                                                  | • ESR = 1 mm/hr                                                         |
| • ESR = 1 mm/hr                                                                | • **MBDA Score = 35**                                                  |

| 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>
<tbody>
<tr>
<td>• Patient had minor hand and wrist pain, 0 swollen and 2 tender joints</td>
<td>• SJC(66) = 0</td>
</tr>
<tr>
<td></td>
<td>• TJC(68) = 2</td>
</tr>
<tr>
<td></td>
<td>• ESR = 2 mm/hr</td>
</tr>
</tbody>
</table>

**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.
Elevated MBDA Score Preceded Clinical Symptoms

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.

Disease Activity Measurements

- SJC(66) = 23
- TJC(68) = 23

January 30, 2012

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.
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.
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.
Summary

- RA causes progressive joint damage, functional impairment, disability, and economic hardship
- 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, but no good predictors at present