Advances in Rheumatoid Arthritis 2020: Diagnosis, Assessment, and Novel Oral therapies

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Rheumatoid Arthritis

- Systemic disease whose predominant manifestation involves a chronic, inflammatory, small joint arthritis
- Affects up to 1% of the US population
- Female:Male predominance of 3:1
- Peak incidence: patients in their 30’s-40’s but can occur at any stage of life
Clinical features of RA

- Most often insidious subacute onset
- Small joint, symmetric inflammatory polyarthritis of diarthrodial joints
  - Morning stiffness (hours) prevalent
  - Improves with activity, worse with inactivity (gelling phenomenon)
  - Joint swelling, joint pain are common
RA: Clinical features

- RA is a chronic and progressive disease

- Chronic disease progression leads to permanent joint deformity, destruction, and disability
Rheumatoid Arthritis: morbidity

- Disease associated with significant morbidity

- Disability costs are high, both in terms of direct and indirect medical costs
  - 35% of patients with 10 years disease duration are work-disabled
    *Arthritis Rheum.* 2008 Mar 27;59(4):474-480

- Significant increase in mortality (SMR 1.4)
  - Surprisingly consistent over 20 years of improved therapy

_Humphreys et al. AC&R 2014_
Improving Outcomes in RA

• Improvement in timely and accurate diagnosis and prognosis

• Treating to defined disease activity targets

• Improvements in therapy
Improving Outcomes in RA

• Improvement in timely and accurate diagnosis and prognosis

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• Improvements in therapy
Early RA: The Window of Opportunity to Intervene
The Window of Opportunity Eventually Closes for Many….

- Chronic disease progression leads to permanent joint deformity, destruction, and disability
- Empirically, RA is a different disease the longer disease activity progresses without effective control
  - More difficult to suppress activity and treat
  - More extra-articular disease?
Rheumatoid arthritis: irreversible damage can occur early in disease course

Radiographic changes in the same joint over time

1 year prior to onset of RA

6 months after onset of symptoms

3 years after onset of symptoms
ACR Criteria for the Classification of Rheumatoid Arthritis 1987

(≥4 criteria required; 1-4 must be present > 6 wks)

• Morning stiffness > 1 hr
• Arthritis of 3 or more joint areas
• Arthritis of wrists, MCPs, and/or PIPs
• Symmetric arthritis
• Rheumatoid nodules
• Serum rheumatoid factor
• Radiographic changes
Limitations of ACR Classification Criteria for the diagnosis of early RA

• Developed for the classification of patients with longstanding disease (for clinical studies, not diagnosis)
  – Many of these features (rheumatoid nodules, for ex) are seen with declining frequency

• For early RA, 1987 classification criteria:
  – Specificity: 90%
  – Limited sensitivity: 40-65%

• Relying on criteria to make a diagnosis of RA can lead to delayed or inappropriate diagnosis
ACR/Eular Classification Criteria 2010

• Joint US-European effort to classify patients with earlier disease for research

• Lacks many of descriptive features of 1987 criteria

• Not as practical for clinical practice: relies on scoring system and algorithms
# 2010 ACR/EULAR Classification Criteria for RA

## Joint Distribution (0-5)

<table>
<thead>
<tr>
<th>1 large joint</th>
<th>0</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-10 large joints</td>
<td>1</td>
</tr>
<tr>
<td>1-3 small joints (large joints not counted)</td>
<td>2</td>
</tr>
<tr>
<td>4-10 small joints (large joints not counted)</td>
<td>3</td>
</tr>
<tr>
<td>&gt;10 joints (at least one small joint)</td>
<td>5</td>
</tr>
</tbody>
</table>

## Serology (0-3)

| Negative RF AND negative ACPA | 0 |
| Low positive RF OR low positive ACPA | 2 |
| High positive RF OR high positive ACPA | 3 |

## Symptom Duration (0-1)

| <6 weeks | 0 |
| ≥6 weeks | 1 |

## Acute Phase Reactants (0-1)

| Normal CRP AND normal ESR | 0 |
| Abnormal CRP OR abnormal ESR | 1 |

≥6 = definite RA

What if the score is <6?

Patient might fulfill the criteria…

- **Prospectively** over time (cumulatively)
- **Retrospectively** if data on all four domains have been adequately recorded in the past
Rheumatoid arthritis

No classification of rheumatoid arthritis
Rheumatoid arthritis
No classification of rheumatoid arthritis

START (eligible patient)

>10 joints (at least one small joint)

4-10 small joints

1-3 small joints

2-10 large (no small) joints

Serology: ++

Serology: +

Duration: ≥ 6 weeks

APR: Abnormal

RA

RA

RA

RA
936 patients with early inflammatory arthritis

Initial evaluation

205 RA by ACR criteria

After 3 years

318 “undifferentiated arthritis” → 127 RA

413 other diagnoses
Factors predictive of progression from undifferentiated arthritis to RA
van Gaalen et al Arth Rheum 50: 709, 2004

<table>
<thead>
<tr>
<th>At initial evaluation</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive rheumatoid factor</td>
<td>1.7 (0.5-5.6)</td>
</tr>
<tr>
<td>Positive anti-CCP antibody</td>
<td>38.6 (9.9-151.0)</td>
</tr>
</tbody>
</table>
Posttranslational modification of proteins: PADI converts arginine to citrulline

Arginine

Citrulline

Peptidyl arginine deiminase (PAD)

$\text{Ca}^{2+}$
RA-associated autoantibodies that recognize peptides containing citrulline

<table>
<thead>
<tr>
<th>Peptide sequence</th>
<th>Antibody recognition</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESSRDGS*RHPRSHD</td>
<td>No</td>
</tr>
<tr>
<td>ESSRDGS*citHPRSHD</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Actual citrullinated antigen(s) targeted in RA is/are not known
Antibodies to citrullinated peptides in RA

- Detected by ELISAs using synthetic cyclic citrullinated peptides (CCP)
- Sensitivity for very early RA: 50%
- Sensitivity for early-later RA: 70-80%
- Specificity for RA: 95-98%
Preclinical autoimmunity in RA: appearance of anti-CCP abs and RF prior to onset of arthritis

Nielen et al Arth Rheum 50: 380, 2004
RF and anti-CCP testing in a cohort of 182 early RA patients

Quinn et al Rheumatology (Oxford) 45:478, 2006
Progression of joint damage in subgroups of early RA

Huizinga et al *Arthritis Research & Therapy* 7: 949, 2005

**Radiographic joint damage score**

- anti-CCP^+ 
- anti-CCP^−
Summary: Clinical utility of the anti-CCP antibody test

- **Diagnosis:**
  - Clinical suspicion of rheumatoid arthritis
  - Early, undifferentiated *inflammatory* arthritis
  - Distinguish RA from other RF* polyarthritis
- **Not useful to monitor disease activity**
- **Best single predictor for destructive disease in patients with early onset RA**
RA: Etiology/Genetics

Manhattan plot from a genome-wide association study of RA

Criswell, LA Immunological Reviews 233: 55, 2010

• 15-20% concordance in monozygotic twins
• RA: 60% heritable contribution
• Most of genetic contribution from Chromosome 6: HLA DR locus
• More copies of HLA risk alleles, higher risk for RA and more severe disease
Gene-environment interaction in RA: Is smoking an environmental trigger?

Evidence for an interaction between smoking and the shared epitope in risk for anti-CCP-positive RA in a European cohort
Periodontitis and the link to RA
Possible culprits

Konig et al. Science Translational Medicine 14 Dec 2016

P. Gingivalis can citrullinate proteins directly

Aggregatibacter actinomycetemcomitans Exo-toxin causes host neutrophils to auto-citrullinate their proteins
### Is rheumatoid arthritis a single disease?

<table>
<thead>
<tr>
<th></th>
<th>RA #1</th>
<th>RA #2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genetic Risk (HLA DR SE)</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>ACPA (? environmental citrullination)</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Erosive dz</td>
<td>+</td>
<td>-</td>
</tr>
</tbody>
</table>
Improving Outcomes in RA

- Improvement in timely and accurate diagnosis and prognosis
- Treating to defined disease activity targets
- Improvements in therapy
RA: Chronic Joint Destruction and Disability – What We Try to Prevent
Joint damage in RA: progressive narrowing and erosion of a MCP joint

At presentation: normal
1 year
5 years
Treatment of early RA

• **Effective treatment** should be started when the diagnosis is made
  – “Effective treatment” = therapies shown to slow joint destruction

• Goal is to induce and then maintain remission
  – Combination of drugs more effective than monotherapy
RA: Traditional Treatment Paradigm

• Pyramid of therapy
  – Start conservatively
  – Gradually ascend the pyramid in order of potency and toxicity of therapy
  – Only the most severely affected patients receive immuno-suppressive, DMARDs
  – DMARD therapy begun only after period of significant delay
Re-Thinking the RA Treatment Pyramid

- Emphasizes earlier diagnosis and initiation of therapy with disease modifying anti-rheumatic drugs
ACR RA Practice Guidelines 2002

• Most patients with Rheumatoid Arthritis should be evaluated expeditiously
• Treatment with DMARD instituted within 3 months of diagnosis
• Goals are to prevent or control joint damage, prevent loss of function, and decrease pain
Tight Control for Rheumatoid Arthritis

- Pre-biologic era study
- Randomly assigned 110 patients to “intensive” vs. usual management
- Every three months, independent blinded metrologist assessed disease activity

Change in disease activity assessed at 18 months
### TICORA Patients

- **Early disease (<2 years)**
- **Active disease**
  - Mean SJC 11-12
  - Mean CRP 38-44 mg/L

<table>
<thead>
<tr>
<th></th>
<th>Intensive group (n=55)</th>
<th>Routine group (n=55)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women</td>
<td>39 (71%)</td>
<td>38 (69%)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>51 (15)</td>
<td>54 (11)</td>
</tr>
<tr>
<td>Disease duration (months)</td>
<td>19 (16)</td>
<td>20 (16)</td>
</tr>
<tr>
<td>Rheumatoid-factor positive</td>
<td>41 (75%)</td>
<td>40 (73%)</td>
</tr>
<tr>
<td>Disease activity score</td>
<td>4.0 (0.0)</td>
<td>4.6 (1.0)</td>
</tr>
<tr>
<td>Swollen joint score (0–44)</td>
<td>12 (4)</td>
<td>11 (4)</td>
</tr>
<tr>
<td>Ritchie articular index</td>
<td>23 (10)</td>
<td>22 (12)</td>
</tr>
<tr>
<td>Pain score (0–100)</td>
<td>62 (20)</td>
<td>59 (20)</td>
</tr>
<tr>
<td>Patient global assessment (0–100)</td>
<td>69 (21)</td>
<td>62 (23)</td>
</tr>
<tr>
<td>Physician global assessment (0–100)</td>
<td>70 (18)</td>
<td>65 (18)</td>
</tr>
<tr>
<td>C-reactive protein (mg/L)</td>
<td>44 (53)</td>
<td>38 (50)</td>
</tr>
<tr>
<td>Erythrocyte sedimentation rate (mm/h)</td>
<td>45 (31)</td>
<td>34 (27)</td>
</tr>
<tr>
<td>Health assessment questionnaire score*(0–3)</td>
<td>2.0 (0.8)</td>
<td>1.9 (0.7)</td>
</tr>
<tr>
<td>Short form-12 physical summary†</td>
<td>28 (7)</td>
<td>28 (8)</td>
</tr>
<tr>
<td>Short form-12 mental health summary†</td>
<td>30 (13)</td>
<td>30 (13)</td>
</tr>
<tr>
<td>Median total Sharp score (IQR)</td>
<td>21.5 (10–39.5)</td>
<td>24.5 (13–25–47)</td>
</tr>
<tr>
<td>Total Sharp score</td>
<td>28 (23)</td>
<td>32 (27)</td>
</tr>
</tbody>
</table>

Data are mean (SD) or number of patients (%), unless otherwise indicated. *0=no disability, 3=maximum disability. †Population mean= 50.

**Table 1: Baseline characteristics**
## What does “Intensive Therapy” Look Like?

<table>
<thead>
<tr>
<th>Standard Therapy</th>
<th>Intensive Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Follow up visits q 3 mo</td>
<td>• Follow up visits q 1 mo</td>
</tr>
<tr>
<td>• DMARD monotherapy used for active disease</td>
<td>• DMARD monotherapy used for active disease</td>
</tr>
<tr>
<td>• Intra-articular injections of TAC allowed</td>
<td>• Intrarticular injections of TAC allowed</td>
</tr>
<tr>
<td>• Changes or additions to therapy were made based upon gestalt</td>
<td>• Changes or additions to therapy were based on formal disease activity (score) &gt; moderate</td>
</tr>
</tbody>
</table>
Mean Disease Activity

Figure 3: Mean disease activity score
Student’s t test used. Intensive vs routine after month 3, p<0.0001. Error bars show SD.
ACR Treatment Guidelines 2008

- Building evidence from trials like TICORA suggests better long term outcomes when treating to a defined target early in disease.

- ACR guidelines encourages regular, formal assessments of disease activity:
  - Similar to hemoglobin A1C for diabetes
  - Several formal disease scores available:
    - DAS28
    - CDAI, SDAI, etc...
    - Vectra-DA biomarker assay

- ACR: Treat to target of mild disease activity or better
**Disease Activity Score 28 Joints**

1. Tender Joint count
2. Swollen Joint Count
3. Patient global disease assessment (visual analog scale from 0-100mm)
4. Serum measure of inflammation (ESR/CRP)

**DAS28**

- CRP: 3.2 mg/dl
- ESR: 30

**DAS28-CRP Activity**

- High

**DAS28-CRP Disease Activity**

- >4.1: High
- 2.7~4.1: Moderate
- <2.7: Low
- <2.3: Remission
DAS: Treating to target

- DAS 28 disease activity cutoffs:
  - DAS28 <2.6 Remission
  - DAS28 2.6-3.2 Mild Activity
  - DAS28 3.21-5.1 Moderate Activity
  - DAS28 >5.1 High Disease Activity
Improving Outcomes in RA

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- Improvements in therapy
DMARD Therapies

• Methotrexate
• Leflunomide (Arava)
• Sulfasalazine
• Azathioprine
• Mycophenolate Mofetil
• “Corticosteroids”
• “Hydroxychloroquine”
• “Minocycline”
RA: Targeted Therapy Approach

- Start with traditional DMARD
- Check to see if low disease activity or better has been attained
- Advance therapy (dose), switch from oral to SQ MTX, or add combination
- Good data that combination DMARDs or combination DMARD + biologic both effective (TEAR trial & CSP 551 RACAT trial)
Families of Biologic Therapies for RA

• Anti-TNF medications
  – Etanercept (TNF decoy receptor fusion protein)
  – Infliximab, Adalimumab, certolizumab, golimumab (variations of anti-TNF antibodies or Fab’)
  – Biosimilar drugs (infliximab-dyyb)

• B-cell depleting agents
  – Rituximab

• T-cell costimulation inhibitors (receptor-ligand)
  – Abatacept

• Inhibitors of IL-6 signaling
  – Tocilizumab (anti IL6 receptor antibody)
  – Sarilumab (anti IL6 receptor antibody)
The Current Pyramid Paradigm

- Early initiation and titration of DMARD
- If incomplete response to DMARD alone, after reasonable titration, addition of combination therapy recommended
“Doc, can I ever stop my RA medicines?”

- Short answer: probably no for most patients

- Long answer: Possibly, for a few lucky patients with RA

- Longer answer: A significant percentage of RA patients may be able to successfully taper their medicines

Tapering or discontinuing anti-TNF therapy


- PRIZE study of early upfront etanercept + MTX followed by taper
  - Those who achieved low dz activity (DAS<3.2) at wk 39 and remission at wk 52 (open label phase) entered randomized double blinded phase
  - 1:1:1 tapered etanercept (1/2 dose) + MTX, PBO+MTX, or double PBO
  - Those with DAS <3.2 at wk 39 had all drug withdrawn through wk 65
PRIZE Results:


- Tapering anti-TNF works for some.
- Sustained remission off therapy achievable in small percentage
Oral Small Molecule Inhibitors: ? New wave of RA therapy

• Not proteins but are small molecules

• Taken orally and can act intracellularly

• “Biologic-like” effects by blocking downstream events initiated by cytokine-receptor engagement

• Emerging term: “Biologic response modifiers”
  – Not organic, complex macromolecules but have similar effects to biological molecules

• First class of kinase inhibitors for RA: JAK inhibitors
  – JAK 1, JAK 2, JAK 3, TYK 2
Cytokine Signaling through Kinases

Current Biologic Therapies

Cytokine: eg. TNF/IL6

Kinases

Transcription
Biologic Effect:
Proliferation
Activation
Cytokine production
Cytokine Signaling through Kinases

Current Biologic Therapies

Cytokine: eg. TNF/IL6

New Kinase Inhibitors

Kinases
Overview of cytokine signaling through Jak and selective inhibition by JAKi’s

- Pan selective JAKi’s have advantage of knocking down multiple cytokine pathways vs more selective JAKi’s or single anti-cytokine therapy (e.g., Anti-TNF)

- Also come with risk of inhibiting important constitutive functions (JAK2 and hematopoiesis)

Pipeline of Oral Small Molecule Inhibitors

- Tofacitinib (PAN JAKi: JAK 1/3 >2 kinase inhibitor)
  - Rheumatoid Arthritis (FDA approved 2012; Failed twice to get approval in Europe until 2017)
  - Now also approved for psoriatic arthritis and ulcerative colitis (2018)
  - Potential future indications: psoriasis, atopic dermatitis, and alopecia areata

- Baricitinib (Pan JAKi: JAK 1/2 kinase inhibitor)
  - FDA approved for RA 2018*

- Upadacitinib (more JAK 1 selective inhibitor)
  - FDA approved 2019

- In development
  - Filgotinib (JAK 1 selective: approval expected in 2020)
40% of MTX naïve patients with active RA achieved a 70% response on Tofacitinib 10 mg vs. 10% on MTX.

Predictable adverse events similar to anti-iL6 therapy
- Liver, neutropenia, lipids, infections, etc.
- Caution that JAK signaling more widespread than for IL6 alone.
Baricitinib: RA-BEACON
Genovese et al. NEJM 2016

Active RA refractory to conventional DMARDs and biological DMARDs
Baricitinib: RA-BEAM
Taylor et al. NEJM 2017

Active RA despite MTX: Comparing Baricitinib to Adalimumab and Adalimumab
Analysis of Spontaneous Postmarket Case Reports Submitted to the FDA Regarding Thromboembolic Adverse Events and JAK Inhibitors

Abril Verden¹ · Mo Dimbil¹ · Robert Kyle¹ · Brian Overstreet¹ · Keith B. Hoffman¹

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Abstract

Introduction The Janus kinase (JAK) inhibitor baricitinib is approved in Europe and Japan for the treatment of rheumatoid arthritis. In April 2017, the US FDA expressed concern about thromboembolic events (deep venous thrombosis [DVT] and pulmonary embolism [PE]) observed in placebo-controlled clinical trials of baricitinib. The European and Japanese labels for baricitinib were recently updated to include a precaution related to potential thromboembolic events in patients at risk. Given that the FDA-approved drugs tofacitinib and ruxolitinib are in the same chemical class, we simulated the application of a Bayesian geometric mean (EBGM) package ‘PhViD’ to estimate the empirical Bayesian geometric mean (EBGM) were used to detect AEs with higher-than-expected reporting rates within the FAERS.

Results We did not find evidence in the FAERS for elevated reporting rates for DVT and PE across the three JAK inhibitors we analyzed. However, multiple drug–AE combinations relating to thromboembolic events had both RORs and EBGM values above 1, indicating a trend toward higher-than-expected reporting rates. For pulmonary thrombosis, the ROR values for ruxolitinib, tofacitinib, and tofacitinib XR were 1.46 (95% confidence interval: 1.05, 2.04), 1.45 (1.05, 2.01), and 2.0.
Baricitinib: Analysis of VTE/PE events

6/997 patients 4 mg @24 wk vs. 0 PBO/2 mg @ 24 wk

Taylor et al. Arth & Rheum 2019 in press

FDA approves amended application for Baricitinib 2018

- FDA originally required new clinical safety trial but changed its mind and accepted amended application with additional secondary analyses of existing clinical trial data

- Black box warning for serious infections and VTE/PE risk

- Only 2 mg (low dose) approved in US. 2 & 4 mg doses already approved in Europe since 2017 and safety surveillance ongoing

- Based upon additional data: Baricitinib should be used with caution in patients with risk factors for DVT/PE:
  - older age, obesity, a medical history of thrombosis, hypercoagulable state, recent surgery or immobilization
Brighter Future for Patients with RA