Rheumatoid Arthritis: What's old and new in 2019

Jonathan Graf, M.D.
Professor of Medicine, UCSF
Division of Rheumatology, ZSFGH
Director, UCSF RA Cohort

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
  - 25% of patients with 10 years disease duration are work-disabled
- Significant increase in mortality (SMR 1.4)
  - Surprisingly consistent over 20 years of improved therapy

Improving Outcomes in RA

- Improvement in timely and accurate diagnosis and prognosis
- Treating to defined disease activity targets
- Improvements in therapy
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

- 1 year prior to onset of RA
- 6 months after onset of symptoms
- 3 years after onset of symptoms

Radiographic changes in the same joint over time

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

<table>
<thead>
<tr>
<th>JOINT DISTRIBUTION (0-5)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>≥6 joints</td>
<td>0</td>
</tr>
<tr>
<td>5-9 joints</td>
<td>1</td>
</tr>
<tr>
<td>4-4 joints (large joints not counted)</td>
<td>2</td>
</tr>
<tr>
<td>3-3 joints (large joints not counted)</td>
<td>3</td>
</tr>
<tr>
<td>≤2 joints (total of large joints)</td>
<td>5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SEROLOGY (0-3)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative RF AND negative ACPA</td>
<td>0</td>
</tr>
<tr>
<td>Low positive RF OR low positive ACPA</td>
<td>2</td>
</tr>
<tr>
<td>High positive RF OR high positive ACPA</td>
<td>3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SYMPTOM DURATION (0-1)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>≤6 weeks</td>
<td>0</td>
</tr>
<tr>
<td>≥6 weeks</td>
<td>1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ACUTE PHASE REACTANTS (0-1)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal CRP AND normal ESR</td>
<td>0</td>
</tr>
<tr>
<td>Abnormal CRP OR abnormal ESR</td>
<td>1</td>
</tr>
</tbody>
</table>

≥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
Diagnosis of early RA by 1987 ACR criteria
van Gaalen et al Arth Rheum 50: 709, 2004

936 patients with early inflammatory arthritis

<table>
<thead>
<tr>
<th>Initial evaluation</th>
<th>After 3 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>205 RA by ACR criteria</td>
<td></td>
</tr>
<tr>
<td>318 “undifferentiated arthritis”</td>
<td></td>
</tr>
<tr>
<td>413 other diagnoses</td>
<td></td>
</tr>
</tbody>
</table>

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

At initial evaluation
<table>
<thead>
<tr>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive rheumatoid factor</td>
</tr>
<tr>
<td>Positive anti-CCP antibody</td>
</tr>
</tbody>
</table>

Posttranslational modification of proteins:
PADI converts arginine to citrulline

RA-associated autoantibodies that recognize peptides containing citrulline

Peptide sequence | Antibody recognition |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>ESSRDGSRHPRSHD</td>
<td>No</td>
</tr>
<tr>
<td>ESSRDGScitHPRSHD</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Actual citrullinated antigen targeted in RA is 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%

RF and anti-CCP testing in a cohort of 182 early RA patients
Quinn et al. Rheumatology (Oxford) 45:478, 2006

RF-CCP+
RF+CCP+
RF+CCP-
RF-CCP-

Preclinical autoimmunity in RA: appearance of anti-CCP abs and RF prior to onset of arthritis
Nielen et al. Arthr Rheum 50: 380, 2004

RA: Etiology/Genetics

• 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
HLA DRB1 alleles and rheumatoid arthritis: shared epitope hypothesis

Note: most common serotype is HLA DR4

<table>
<thead>
<tr>
<th>DRB1 allele</th>
<th>70</th>
<th>71</th>
<th>72</th>
<th>73</th>
<th>74</th>
</tr>
</thead>
<tbody>
<tr>
<td>0101</td>
<td>Q</td>
<td>R</td>
<td>R</td>
<td>A</td>
<td>A</td>
</tr>
<tr>
<td>0401</td>
<td>Q</td>
<td>K</td>
<td>R</td>
<td>A</td>
<td>A</td>
</tr>
<tr>
<td>0404</td>
<td>Q</td>
<td>R</td>
<td>R</td>
<td>A</td>
<td>A</td>
</tr>
<tr>
<td>0405</td>
<td>Q</td>
<td>R</td>
<td>R</td>
<td>A</td>
<td>A</td>
</tr>
<tr>
<td>0408</td>
<td>Q</td>
<td>R</td>
<td>R</td>
<td>A</td>
<td>A</td>
</tr>
<tr>
<td>1402</td>
<td>Q</td>
<td>R</td>
<td>R</td>
<td>A</td>
<td>A</td>
</tr>
<tr>
<td>1001</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>A</td>
<td>A</td>
</tr>
<tr>
<td>CONSENSUS</td>
<td>Q/R</td>
<td>R/K</td>
<td>R</td>
<td>A</td>
<td>A</td>
</tr>
</tbody>
</table>

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

- P. Gingivalis can citrullinate proteins directly
- Aggregatibacter actinomycetemcomitans
  - Exo-toxin causes host neutrophils to auto-citrullinate their proteins
Among SE+ RA patients, those who are CCP+ have radiographic progression

Van Gaalen et al. Arthritis and Rheumatism 2004;50;7:2113-2121

CCP+ patients have progression of damage whether SE+ or not

Huizinga, Citrullin et al. Arthritis and Rheumatism 2005;52;11:3433-3438

Progression of joint damage in subgroups of early RA

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

- Anti-CCP status
  - Anti-CCP positive RA patients are unique compared to anti-CCP negative patients
    - Shared epitope positive compared to controls
      - No additional contribution to risk of developing RA from SE independent of CCP status (data not shown)
    - More erosive disease
    - More progressive course of disease (radiographically)

- Is rheumatoid arthritis a single disease?
  - RA #1
    - SE +
    - CCP +
    - Erosive dz +
  - RA #2
    - SE -
    - CCP -
    - Erosive dz -

- Anti-CCP status
  - Anti-CCP positive RA patients are unique compared to anti-CCP negative patients
    - Shared epitope positive compared to controls
      - No additional contribution to risk of developing RA from SE independent of CCP status (data not shown)
    - More erosive disease
    - More progressive course of disease (radiographically)
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**

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 immunosuppressive, 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

What does "Intensive Therapy" Look Like?

**Standard Therapy**
- Follow up visits q 3 mo
- DMARD monotherapy used for active disease
- Intra-articular injections of TAC allowed
- Changes or additions to therapy were made based upon gestalt

**Intensive Therapy**
- Follow up visits q 1 mo
- DMARD monotherapy used for active disease
- Intra-articular injections of TAC allowed
- Changes or additions to therapy were based on formal disease activity (score ≥ moderate)

**TICORA Patients**

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

**Mean Disease Activity**

![Mean disease activity graph](image-url)
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
    • CDAD, SDAI, etc...
    • Vectra-DA biomarker assay

• ACR: Treat to target of mild disease activity or better

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

• Improvement in timely and accurate diagnosis and prognosis

• Treating to defined disease activity targets

• Improvements in therapy
DMARD Therapies

- Methotrexate
- Leflunomide (Arava)
- Sulfasalazine
- Azathioprine
- Mycophenolate Mofetil
- "Corticosteroids"
- "Hydroxychloroquine"
- "Minocycline"

Methotrexate

- Standard RA DMARD therapy
- Clinical Response: 3-6 weeks
- Dosed one day per week, 7.5mg-20mg total
- Toxicity profile
  - Hepatotoxicity – transaminitis
  - Myelosuppression – especially lymphocytes
  - Hypersensitivity pneumonitis and interstitial lung disease
  - Mucosal irritation – Use concurrent folate supplements
- Monitor CBC, LFTs q 4 weeks until achieve stable dose then q 4-8 weeks as long as take medication
- Bioavailability is variable: 20-80% (parenteral form available as weekly SQ injection)

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 & CSP 551 RACAT)
Why Move Towards Combination Regimens with Biologics??
Klareskog L. et al. TEMPO Lancet 2004

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?"
OPTIMA 2014 PRIZE 2014

- 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

---

**Families of Biologic Therapies**

- **Anti-TNF medications** (5 total)
  - 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 IL-6 receptor antibody)
- **IL-1 Inhibitors** (anti-IL1 directed therapy)
  - Anakinra

---

**Brighter Future for Patients with RA**

- **Families of Biologic Therapies**
  - **Anti-TNF medications** (5 total)
    - 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 IL-6 receptor antibody)
  - **IL-1 Inhibitors** (anti-IL1 directed therapy)
    - Anakinra
Practical issues to consider in patients on long term anti-TNFs: Pharmacokinetics...

- Anti-TNF medications have long half lives
- This is important for duration of the biologic effect
- Also important in case someone develops a side effect or infection while on one of these medicines
  - Etanercept 4.25 days
  - Infliximab 8-12 days
  - Adalimumab 14 days
- Many patients, especially those on IV therapy, (infliximab, rituxan, etc…) may not mention to their MD that they are on therapy

Contraindications

- History of latent tuberculosis unless/until they have completed an adequate courses of prophylactic therapy (Duration up for debate)
- Active acute or chronic infections (HCV exception)
- Active or suspected malignancies.
- Anti-TNFs are generally contraindicated in patients with moderate or severe congestive heart failure (some have black box warning)
- History of demyelinating disease
- Use of live vaccine in previous 2 weeks

Anti-TNFs: Adverse Events

- Increased risk of infections! (OR of 2.0 for serious infection in large meta analysis published in JAMA 2006)
  - Most common URIs
  - Problematic: mTB and other intracellular organisms for which TNF is necessary for immune containment
- Increased malignancy risk: Controversial and contradictory data:
  - May worsen symptoms of congestive heart failure.
Infliximab and TB


56% Extra Pulmonary TB
24% Disseminated disease
Patients don’t make granulomas (atypical appearance)
Average onset 12 weeks after initiation (3-4th dose)

Specifics: Hepatitis B

• Patients with chronic hepatitis B infections are at risk for re-activation and liver injury
• Risk is highest for those who are hepatitis B surface antigen positive and/or DNA positive
• Risk is lowest for those who are surface antigen negative and surface antibody positive

Hepatitis B Recommendations:

• We screen all patients for HBV serologies
• Follow LFTs in "carriers" who are Hep B Core Ab+ and ensure that viral load is undetectable
• Avoid anti-TNF therapy in patients who have chronic active infection (Hep B Sag+) unless:
  • If use anti-TNFs in Hep B Sag+ patients:
    – we initiate anti-Hep B therapy (RT inhibitors)
    – Follow Hep B DNA PCR for log changes in viral copies

Specifics: Anti-TNFs and Malignancy

• Large meta-analysis suggested an OR 3.3 for all malignancies in patients using anti-TNF, especially “high doses.” (Bongartz et al., JAMA 2006)
• Longitudinal analysis of 20,000 patients from the National Databank of Rheumatic Diseases found no increased risk of lymphoma compared to general population or those with RA (Wolfe et al., A&R 2007)
• Two studies published in 2011 (including large Danish registry) corroborate lack of evidence linking cancer to anti-TNF therapy in adult RA patients
When patients fail anti-TNF therapy…

- Up to 30% of patients fail to respond or lose response to anti-TNF therapy
- Additional patients are intolerant or have contraindication to anti-TNF therapy
- There are now many other biologic therapies available

When Patients fail anti-TNF therapy:

- B-cell depleting agents
  - Rituximab
- T-cell costimulation inhibitors (receptor-ligand)
  - Abatacept
- Inhibitors of IL-6 signaling
  - Tocilizumab (anti IL-6 receptor antibody)
- IL-1 Inhibitors (IL-1 cytokine receptor decoy)
  - Anakinra

Future directions in RA therapy

- Oral small molecule biologic inhibitors have now arrived on the scene.
- Block intracellular cell signaling events that occur after a cytokine binds to its receptor.
- Proteins called kinases mediate a cascade of signals that result in DNA transcription
- Biologic effect: Immune cell activation, differentiation, and proliferation

Cytokine Signaling through Kinases

- Current Biologic Therapies
- Cytokine: eg. TNF
- Kinase
- Transcription
- Biologic Effect
Cytokine Signaling through Kinases

Cytokine:
eg. TNF

Current Biologic Therapies

New Kinase Inhibitors


Tofacitinib (Xeljanz) FDA approved Nov. 2012
Approved for use in Europe: 2017

Baricitinib: RA-BEACON
Genovese et al. NEJM 2016

Baricitinib in Patients with Refractory Rheumatoid Arthritis

Taylor et al. NEJM 2017

Baricitinib versus Placebo or Methotrexate in Rheumatoid Arthritis

Tofacitinib (Xeljanz) FDA approved Nov. 2012
Approved for use in Europe: 2017
Baricitinib: Yet to receive FDA approval

Extra Slides RCAT
1. Patients randomized to triple DMARDs vs. etanercept + MTX and were then assessed at 24 weeks
2. Patients whose DAS28 did not improve by at least 1.2 were switched to other arm
3. Majority stayed on their original treatment
4. Switching equal between arms
5. Disease activity non-inferior between two groups