Rheumatoid Arthritis Update 2014

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Rheumatoid Arthritis

- Chronic, inflammatory, predominantly small joint arthritis
- Affects up to 1% of the US population
- Female:Male predominance of 3:1
- Disability costs are high, both in terms of direct and indirect medical costs
  - 35% of patients with 10 years disease duration are work-disabled
  - Decline from 50% rate reported in 1987
  

RA: Chronic Joint Destruction and Disability – What We Try to Prevent

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

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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?

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)
  - Classification criteria revised in 2010 to allow for the study of patients with earlier disease, but not as descriptive
- 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

Diagnosis of early RA by 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>
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<tbody>
<tr>
<td>205 RA by ACR criteria</td>
<td></td>
</tr>
<tr>
<td>936</td>
<td></td>
</tr>
<tr>
<td>318 &quot;undifferentiated arthritis&quot;</td>
<td></td>
</tr>
<tr>
<td>127 RA</td>
<td></td>
</tr>
<tr>
<td>413 other diagnoses</td>
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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>Factor</th>
<th>OR (95% CI)</th>
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<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>
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Posttranslational modification of proteins:
PADI converts arginine to citrulline
RA-associated autoantibodies that recognize peptides containing citrulline

<table>
<thead>
<tr>
<th>Peptide sequence</th>
<th>Antibody recognition</th>
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<tbody>
<tr>
<td>ESSRDGSRHPRSHD</td>
<td>No</td>
</tr>
<tr>
<td>PADI</td>
<td></td>
</tr>
<tr>
<td>ESSRDGScitHPRSHD</td>
<td>Yes</td>
</tr>
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Actual citrullinated antigen 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

Preclinical autoimmunity in RA: appearance of anti-CCP abs and RF prior to onset of arthritis
Nielen et al Arth Rheum 50: 380, 2004
Development of better tools to predict disease severity

Is it possible to predict which patients require more aggressive therapy up front?

Classic Predictors of Disease Severity

- More difficult to treat, destructive, extra-articular disease:
  - Rheumatoid factor positive
  - Erosive disease
  - Genetic factors
    - HLA class II DR4 and other molecules that contain "shared epitope"
    - Not practical to genotype all patients

<table>
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<tr>
<th>HLA DRB1 alleles and rheumatoid arthritis: shared epitope hypothesis</th>
</tr>
</thead>
<tbody>
<tr>
<td>amino acid position on the DRβ chain</td>
</tr>
<tr>
<td>DRB1 allele</td>
</tr>
<tr>
<td>0101</td>
</tr>
<tr>
<td>0401</td>
</tr>
<tr>
<td>0404</td>
</tr>
<tr>
<td>0405</td>
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<tr>
<td>0408</td>
</tr>
<tr>
<td>1402</td>
</tr>
<tr>
<td>1001</td>
</tr>
<tr>
<td>CONSENSUS</td>
</tr>
</tbody>
</table>

Presence of CCP antibodies, not SE, confers risk for more aggressive RA

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

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

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RA: Chronic Joint Destruction and Disability – What We Try to Prevent

Joint damage in RA:
progressive narrowing and erosion of a MCP joint

Irreversible damage can develop within months of onset of RA

Radiographic changes in the same joint over time
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
ACR Treatment Guidelines 2008

- Encourages more formal assessments of disease activity
  - Similar to hemoglobin A1C for diabetes
  - Several formal disease scores available:
    - DAS28
    - CDAI, SDAI, etc...
    - Vectra-DA biomarker assay
- Building evidence (not shown) suggests better long term outcomes when treating to a defined target early in disease
- 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 Moderate Activity
  - DAS28 3.21-5.1 Moderate Activity
  - DAS28 >5.1 High Disease Activity

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DMARD Therapies

- Methotrexate
- Leflunomide (Arava)
- Sulfasalazine
- Azathioprine
- Mycophenolate Mofetil
- “Corticosteroids”
- “Hydroxychloroquine”
- “Minocycline”
Combination DMARD Therapies: Some Step Up, Others Step Down

- Start with traditional DMARD
- Check to see if low disease activity or better has been attained
- Advance therapy with combination regimen
- Increasing use of combination therapy with DMARDs and Biologic medication
- Controversial whether upfront combo or step up therapy better long-term

Why Move Towards Combination Regimens with Biologics??

The Current Pyramid Paradigm

- Early initiation and titration of DMARD
- If incomplete response to DMARD alone, after reasonable titration, addition of biologic recommended

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')
- 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
### Families of Biologic Therapies

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### 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+, even if also SAb+
- 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

[Diagram showing cytokine (e.g., TNF) binding to receptors, followed by kinases mediating a cascade, leading to transcription and biologic effect.]
Cytokine Signaling through Kinases

Current Biologic Therapies → Cytokine: eg. TNF → Kinases

Future Therapies

Brighter Future for Patients with RA

The Safety and Efficiency of a JAK Inhibitor in Patients With Active Rheumatoid Arthritis: Results of a Double-Blind, Placebo-Controlled Phase II Trial of Three Dose Levels of CPX-606/543 Versus Placebo

Kremer et al. A&R July 2009