Annual Rheumatology & Therapeutics Review for Organizations & Societies
RA Pearls and Controversies
Pre-Clinical Rheumatoid Arthritis
Does Smoking Increase the Odds of Non-response to Rx in Early RA

- 2 RA registries suggest smoking and pack-yrs exposure are associated with decreased Rx responses in RA
- Swedish registry, population based study of incident RA and response to their first MTX or TNF inhibitor based on smoking history
- @3 mo NonResp <0.6 △DAS or DAS >5.1

<table>
<thead>
<tr>
<th>MTX– Response @ 3 mos.</th>
</tr>
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<tbody>
<tr>
<td><strong>Smoker</strong></td>
</tr>
<tr>
<td>Never</td>
</tr>
<tr>
<td>Past</td>
</tr>
<tr>
<td>Current</td>
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</table>

<table>
<thead>
<tr>
<th>TNF inhib - Response @ 3 mos</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Never smoker</strong></td>
</tr>
<tr>
<td>Never smoker</td>
</tr>
<tr>
<td>Current smoker</td>
</tr>
</tbody>
</table>

Saevarsdottir S, ACR 2009
Oral Microbiota and Gingivitis in RA

- Gingivitis associated with RA risk and severity
- Citrullinated proteins and PAD activity is present in oral mucosa in non-RA
- Porphyromonas gingivalis is found increased in RA patients using high throughput DNA sequencing 16s rRNA

Periodontal disease in RA

1. Sher J, et al. ACR 2010, Atlanta #1390
2. Bingham C, et al. Ibid #1074
Does Obesity Impair Response to TNF inhibitors?

- 91 active RA (DAS28 ≥3.2) MTX – IR
- BMI (17.4-42.2) correlate w/ DAS28 (r=0.34)
  - CCP+ had higher BMI (29 vs 25, p=0.003)
- 61/91 pts responded to INF (3 mg/kg)
  - Inverse correlation BMI & DAS resp r -0.21, p 0.055
  - BMI higher in NR (26.8) than resp (25.5)
- RA patients with a high BMI responded less well to infliximab – despite dosing on mg/kg basis

Obesity & RA

- Proinflammatory Adipokines: Leptin & Resistin
- Steroid use, immobility & lifestyle change?
- Microbiome change?
- Risk factor for RA disease onset and severity
- Obese less likely to respond to DMARDs, TNFi
- Obese have less erosions (RA) & BMD loss (OP)
- Increased morbidity during TKR/THR
- Independent association with impaired QOL in RA
- Paradoxical effect of obesity on survival in RA

Epigenetics and RA

- GWAS has shown that genetic polymorphisms are not solely responsible for the risk of developing rheumatoid arthritis
- Epigenetics: modifications of DNA and histones, subject to environmental influences and regulate gene expression.
  - DNA methylation (inhibits transcription factor binding → repressed transcription; affected by factors e.g. diet; esp. kids)
  - Histone modification
    - PADI4 mediated histone citrullination → chromatin decondensation; PMN inflammation, pluripotent cells
  - Micro-RNA – negatively regulates protein translation via antisense RNA-RNA interaction

Microbiome and the Risk of RA

- We are 10% Human and 90% microbial DNA
- Human-assoc. microbial communities have diverse effects:
  - Digestion
  - immune system maturation
  - polysaccharide production
  - toxin degradation
  - pathogen defense
- Implicated microbiomes
  - Gingival mucosa
  - Gut microbiome
  - Lung
  - Skin

Altered Lung Microbiome in At-Risk CCP+  

- Preclinical phase in RA wherein triggers predict outcome  
- 13 arthritis-free CCP+ pers. compared to 9 healthy controls  
- Microbiome analysis with 16SrRNA gene amplification and 454 pyrosequencing on induced sputum samples  

- Results: show different lung microbiota  
  - More abundant Hemophilus (2.0 vs. 0.6%, P = 0.01) and Streptococcus (30.4 vs. 18.0%, P = 0.07)  
  - Lower for Prevotella (12.4 vs. 25.0%, P = 0.07).  
  - 9/13 CCP+ had inflammatory airway dz on lung imaging  

- Possible mechanistic link between the lung microbiome, mucosal inflammation, and RA-related autoimmunity  

Probiotic Shows Benefit in RA

- DBRPCT of Probiotic supplementation on RA activity
- 46 patients randomized to receive Probiotic vs Placebo
- Significant difference between the two groups at week 8
  - Disease activity ($P < 0.01$).
  - Serum TNF-α, IL-6, IL-12 significantly decreased ($P < 0.05$);
  - IL-10 was increased ($P < 0.05$) in the probiotic group
  - IL-1 β not affected ($P = 0.22$)

Gout and Rheumatoid Arthritis
A Negative Association?

- Unclear how often these two conditions coexist
- Two studies estimate RA occurs in 2-3.8% of gout pts.

<table>
<thead>
<tr>
<th>Gout</th>
<th>Criterion</th>
<th>Rheumatoid</th>
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<tbody>
<tr>
<td>↑sUA</td>
<td>Biomarker</td>
<td>CCP+/RF+</td>
</tr>
<tr>
<td>Scooped out w/ overhanging</td>
<td>Erosions</td>
<td>Marginal, “rat bite”</td>
</tr>
<tr>
<td>May break skin</td>
<td>Tophi/Nodule</td>
<td>Never break thru</td>
</tr>
</tbody>
</table>

- Sporadic case reports in literature over 30 yrs
- Patients with Co-Present Gout & RA
  - Older, predominantly male w/ higher serum creatinine and uric acid and Lower Hgb. RF & CCP+ is rare
  - 75% a gout Dx preceded RA
  - Gout attacks may occur while stable on DMARD Rx

Kitas Rheumatology 2007;46:1466-7
Kuo Clin Rheumatol. 2008;27:231
Rizzoli J Rheumatol. 1980 7:316.
The (+) Serologic Test Consult and Risk of RA or SLE

**+ANA Consults**
- 4-5% of population is RF+
- RA prev 0.5 – 2.0%
- 20 million USA w/ RF+
  - 1.3 million w/ RA
  - 1/20 chance that RF+ person will have RA

**+ Rf (+CCP) Persons**
- 4-5% of population is ANA+
- SLE prev <1 per 1000-10K
- 20 million USA ANA+
  - 300,000 w/ SLE
  - 1-2 per 100 chance that ANA+ will have lupus

**+ANA: PPV**
- 2.1% for lupus
- 9.3% autoimmune Dz

No Rheum dz w/ ANA <1:160

Abeles A. Am J Med. 2013 Apr;126(4):342-8
Elevated RF Increases the Risk of RA

- Prospective study: Denmark 9712 healthy population aged 20-100 yrs without a dx of RA; 28 yr F/U.
- During 187 659 PYs of F/U → 183 developed RA
- RF levels : no incr. w/ Age
- Doubling of RF → 3.3 fold inc
- Higher titers = Shorter time to RA (15 yrs @25; 7 yrs @ >100)
- Highest 10 yr risk of RA (32%) was in women, 50-69 yrs, who smoked, w/ +RF >100 IU/mL

Nielsen SF BMJ. 2012 Sep 6;345
Carbamylated Abs and Risk of RA

- Carbamylation involves the conversion of Lysine to homocitrulline (by MPO, inflammation)
- Anti-carbamylated Abs present in 33-43% RA pts
  - Do not overlap w/ ACPA+ pts
- Anti-CarP Abs (+)
  - Correlates w/ Xray damage
- Arthralgia pts w/ anti-CarP
  - Likely to develop RA

Seropositive vs. Seronegative

- More efficacy
  - RTX, ABA, MTX
- More toxicity
- Differences due to
  - Higher Activity?
  - RA Homogeneity
  - Misdiagnosed RF neg – SpA, IBD, CPPD, etc
Rituximab (REFLEX): EULAR Responses Based on RF/CCP status

- Significantly more patients on RTX achieve ACR20 and EULAR responses than PBO
- Seronegative RF & CCP- responded less well
- A post hoc analysis of TNF failures revealed that radiographic response in anti-CCP2 negative patients is not significant.²

No. of patients is small: RTX 33; PBO 21

PBO
RTX
PBO
RTX

% patients EULAR Mod/Good at Week 24

RF/Anti CCP+
Either or both

RF/Anti CCP-

PBO
RTX

Tak P-P, et al. EULAR 2007, Barcelona, #FRI0192; Cohen S, et al. ibid, SAT0002
Identifying at-risk populations is the first step in “Prevention” of RA.

MTX Failures: ACR20

O'Dell 2000
MTX: The Drug Rheumatologists Love & Patients Hate

• 55 yoWF w/ new seropositive RA and 6 swollen joints is started on MTX 15 mg/wk & folate 1 mg/d. By wk 6 her SJC = 3 and MTX ↑ 20mg/wk. Wk 12 SJC =1

• >wk 12 pt c/o feeling “bad” for 1-2 post MTX
  – Blahs, quesy, HA, anorexia→moves to Sat dose

• How do you manage?
  – ↑△ Folate? △MTX to sc/IM? Reduce dose?
  – Use vitamins? Cough syrup?
RA: Optimizing Methotrexate

- Parenteral vs Oral
- Split dose oral vs parenteral
  - Bioavailability
- Polyglutamation
- CNS Toxicity
- Oral/GI toxicity
Optimal Dosing and Use of MTX

- Metanalysis of 38 papers
- 25 mg/wk (fast escalation to 30 mg/wk) ↑ effect sizes but more GI AE (vs. 5–15 mg/wk)
- 15 mg/wk parenteral vs po MTX assoc. with higher clinical efficacy but more toxicity withdrawal
- IF fail 15–20 mg/wk po → switching to 15 mg/wk IM with subsequent dose escalation did not increase efficacy
- Optimal Dosing? Start at 15 mg/wk orally, escalate 5 mg/month to 25–30 mg/wk, and switch to subcutaneous MTX if there is an insufficient response

Study Design and Results

- **Purpose**
  - Compare the relative bioavailability of methotrexate delivered by autoinjector with oral MTX

- **Design**
  - 49 adults already receiving MTX were given 10, 15, 20, or 25 mg MTX based on current dose and disease control via random assignment to:
    - Oral MTX
    - MTX autoinjector (abdomen)
    - MTX autoinjector (thigh)

- **Primary end point**
  - Pharmacokinetic analysis

**Pharmacokinetic Analysis**

Schiff M, et al. ACR 2013 #796
Increase MTX Bioavailability with Split Oral Doses

- 10 RA patients taking a stable dose (25–35 mg weekly) of MTX
- MTX PK studied w/ single vs split dose
- Split dose bioavailability was 28% higher (p =0.007).
- bioavailability after
  - single-dose - 0.76
  - split-dose MTX - 0.90
- PO split dose bioavailability equal to parenteral dosing

Hoeckstra  J Rheumatol March 2006 33(3):481-485
MTX: Mucosal Toxicity

- Mucositis, Nausea, Vomiting, Diarrhea, colonic ulcerations (rare)
- po MTX + Rat = hemorrhagic enterocolitis
- No efficacy of folate supplementation
- Vitamin A: po 8000 IU EVERY DAY
Methotrexate has been reported to cause fetal death and/or congenital anomalies...not recommended for women of childbearing potential unless there is clear medical benefits > considered risks.

- Pregnant women with PSO or RA should not receive methotrexate.
- T ½ is approximately 3-10 hrs
- Do not start MTX until pregnancy is excluded; counsel pts on the serious risk to the fetus.
- Pregnancy should be avoided if either partner is receiving methotrexate; during and for a minimum of three months after therapy for male patients, and during and for at least one ovulatory cycle after therapy for female patients.
- MTX: embryotoxicity, abortion & fetal defects in humans. Reported to cause infertility, oligospermia and menstrual dysfunction, during and for a short period after MTX cessation.

## Methotrexate Use in Pregnancy

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<tbody>
<tr>
<td><strong>Dose (mg)</strong></td>
<td>Low</td>
<td>7.5-42</td>
<td>7.5-10</td>
<td>10.5</td>
<td>5-15</td>
<td>Low</td>
</tr>
<tr>
<td><strong># Exposed</strong></td>
<td>31</td>
<td>14</td>
<td>8</td>
<td>23</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td><strong>Miscarriage</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N (%)</td>
<td>7 (23%)</td>
<td>4 (29%)</td>
<td>3 (38%)</td>
<td>4 (17%)</td>
<td>1 (25%)</td>
<td>1 (100%)</td>
</tr>
<tr>
<td><strong>Live births</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N (%)</td>
<td>23 (74%)</td>
<td>10 (71%)</td>
<td>5 (62%)</td>
<td>19 (83%)</td>
<td>3 (75%)</td>
<td>0</td>
</tr>
<tr>
<td><strong>Birth defect</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N (%)</td>
<td>3 (9%)</td>
<td>1 (7%)</td>
<td>0</td>
<td>1 (4%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
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<td></td>
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<td>5/81 = 6.2%</td>
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PROMPT Trial

- 110 UA patients from Dutch Early Arthritis Clinics
  - Sxs <2 years; 1958 ARA criteria for “probable RA”
- Double-blind RCT: MTX vs. placebo
  - MTX started at 15 mg/week; -> 30 mg/wk to achieve DAS <2.4
  - After 12 months, MTX tapered off
  - Anti-CCP status known post-study
- Outcomes: Xray outcome and evolution to RA (1987)

Van Dongen H, et al. EULAR, Amsterdam 2006, #OP0001
PROMPT Trial

Kaplan-Meier survival curve for not developing RA

Time to diagnosis RA (months)

Cumulative survival (%)

Total group
n=110
p=0.02
MTX group
Placebo group

Survival per anti-CCP status

Anti-CCP pos group (n=27) p=0.0001
Anti-CCP neg group (n=83) p=0.51

MTX group
Placebo group

Radiographic progression

Radiographic progression (Sharp/van der Heijde score)

Total group
n=102
p=0.15
Placebo group
MTX group

Anti-CCP pos group (n=27) p=0.03
Anti-CCP neg group (n=83) p=0.46

Van Dongen H, et al. EULAR, Amsterdam 2006, #OP0001
DMARD/TNFfi Use with Hepatic Dz

- Contraindicated with Hepatic Disease Hx
  - MTX
  - Leflunomide
  - NSAIDs
  - Acetaminophen
  - Azathioprine
  - Sulfasalazine
  - Mycophenolate
- Contraindicated w/HBV+
  - Rituximab
  - TNF inhibitors
  - MTX
  - Leflunomide
- Transplant drugs w/ hepatitis
  - Glucocorticoids
  - Azathioprine
  - Mycophenolate
  - Cyclosporine
- Probably Safe w/ HCV+
  - Glucocorticoids
  - Hydroxychloroquine
  - TNF inhibitors
  - Gold Salts
- Unknown Safety w /HCV+
  - Abatacept
  - Rituximab
What Rheumatologists Know, Measure & Do

- Metrics in Practice – change over time
- T2T & Outcomes
- Changing Therapies in a Timely Manner
What Measures Do You Routinely Perform in the Care of Your RA Patients?

- GAS
- RAPID
- CDAI
- SDAI
- Ritchie
- ACR20
- DAS

N=446 USA Rheums  CushJJ. ACR 2008
What Measures Do You Routinely Perform in the Care of Your RA Patients?

- GAS
- RAPID
- CDAI
- SDAI
- ACR20
- DAS

N=446 USA Rheums  CushJJ. ACR 2008
US Rheumatologists: How Often Do You Achieve ACR20 or Remission in Your RA Patients?

Cush JJ. ACR 2008  2/08 Survey US Rheums n=445
Real World Observational Studies in RA

Weisman MH et al. EULAR; June 9–12, 2004; Berlin, Germany; abstract OP0042.
RADIUS I and RADIUS II Outcomes

Summary of ACR (3 of 4 With Improvement) Responders at 12 Months Post Baseline (LOCF) by Study

Patients Achieving ACR Score (%)

How Often Do RA Patients Get DMARDs?

- “Every pt w/ established, active RA must be Rx w/ DMARD”
- 5864 PA Medicare and PACE patients w/ RA 1996-2004
- Seen by Rheum? 33% in 1st 12 mos (baseline period)
  - 90% in 12 month follow-up period
- DMARD use
  - 70% were NOT on any DMARD; 27% NO Rx at all
  - 30% overall (53% if seen by Rheum in baseline period)
    - Only 8% was Rheum primary Prescriber of DMARD Rx
  - DMARD use increased over time
    - Rheum ≥1 visit 41% (1996) → 70% (2003)
  - Elderly less likely to receive DMARDs (more likely NSAIDs)
  - Patients w/ comorbidity more likely to receive DMARD Rx

No DMARD Changes Despite Activity

- RADIUS database - 9873 RA patients
- Examined pts with moderate activity ≥ 5 TJC/SJC
  - N = 6745 analyzed
  - % with NO change in DMARD Rx
    - @ 6 mo  67%
    - @ 12 mo  48%
    - @ 18 mo  38%
- 74% of these pts were on biologics
  - All improved, but:
    - 25% did not achieve < 5 TJC/SJC
    - 54% did not achieve Pain VAS < 3
- Measuring does not ensure optimal outcomes

Changing DMARDs Rx In Practice

- 568 RA pts – 6159 visits/ 1 yr
- % of DMARD changes vs. activity
  - **DMARD ever**
  - 377 Severe RA 94%
  - 149 Moderate RA 81%
  - 42 Mild RA 76%
- Mean: age 54 yrs, 78% F, 83% white, HAQ 0.88, RADAI 4.4 (0-10), 6.9 rheum visits/yr
- Severe dz for 6-9 mos → 57-74% had DMARD changes
- Despite active Disease, DMARD changes lag

Rheumatologists Are Slow to Change (DMARDs)

- Provider Prescribing practices prior to visits before 6/15/08. Pts in remission or LDAS were excluded. 427 patients analyzed.
- Despite moderate-high disease activity; few Rx changes

<table>
<thead>
<tr>
<th>Activity ⇒</th>
<th>MTX monotherapy</th>
<th>≥ 2 prior DMARDs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Moderate N 130</td>
<td>High N 154</td>
</tr>
<tr>
<td>Biologic start</td>
<td>9%</td>
<td>8%</td>
</tr>
<tr>
<td>DMARD start</td>
<td>5%</td>
<td>1%</td>
</tr>
<tr>
<td>No Change</td>
<td>76%</td>
<td>68%</td>
</tr>
<tr>
<td>No DMARD</td>
<td>10%</td>
<td>23%</td>
</tr>
</tbody>
</table>

Despite poor prognostic findings and use of metrics – Rheumatologists do not aggressively optimize DMARD therapy

Harrold et al. ACR 2009