Rheumatoid Arthritis: New and Emerging Agents and Trends

Arthur Kavanaugh, MD
Director, Center for Innovative Therapy
Professor of Medicine
Division of Rheumatology, Allergy, and Immunology
University of California San Diego
La Jolla, CA
Arthur Kavanaugh: Disclosures

- Abbott
- Amgen
- Astra-Zeneca
- Biogen-Idec
- BMS
- Celgene
- Centocor
- Genentech
- TREG Consultants LLC
- ITN
- LCTC
- MedImmune
- NIH
- Roche
- Sanofi-Aventis
- Teva
- UCB

RA: Therapeutic Interventions

- Adjunctive (NSAIDs / COX-2 / Corticosteroids), analgesics, PT/OT, etc
- DMARDs
  - MTX, LEF, SSZ, HCQ >> CsA, Min, IM gold, etc
  - Tofacitinib (Jak3/1 inhibitor)
- Biologics
  - TNF-Inhibitors: etanercept, infliximab, adalimumab, certolizumab pegol, golimumab
  - IL-1 Inhibitors: anakinra (IL-1ra); rilonacept (IL-1-TRAP), canakinumab
  - Abatacept (CTLA-4-Ig)
  - Rituximab (α-CD20 mAb)
  - Tocilizumab (α-IL-6R mAb)
- Experimental / Emerging
  - other B cell (α-CD22 [epratuzumab]: α-BAFF/BLyS,TACI, APRIL)
  - other IL-6 inhibitors (sirukimab, sarilumab etc)
  - kinase inhibitors (Syk [fostamatinib], Jak, MEK, etc)
  - α-IL-12/23 mAb (ustekinumab, briakinumabetc)
  - α-IL-17 (secukinumab, ixekizumab, brodalumab)
  - biosimilars
**TNF Inhibitors**

Chimeric monoclonal antibody  
Humanized monoclonal antibody  
Human monoclonal antibody  
Humanised Fab' fragment  
Human receptor / Fc fusion protein

- infliximab IgG1  
- adalimumab IgG1  
- golimumab IgG1  
- certolizumab pegol  
- etanercept IgG1

**Current Status: TNF-inhibitors**

- Most patients respond, (some do not) - some achieve “remission”
- Clinical efficacy usually requires continued therapy (i.e. no tolerance or “cure”); ?, especially in early disease, can TNFi be tapered or stopped after ‘induction’ into remission or low disease activity
- TNFi highly effective in AS, PsA, psoriasis. In uveitis, psoriasis, mAb appear more effective. ? mAb more effective in IBD (Crohn’s disease, ulcerative colitis). mAb ? less safe (e.g. TB). ? Dose
- TNFi not effective in sepsis, CHF, Wegener’s, PMR/TA, sarcoid, Sjogrens
- Biosimilar TNF-i: Likely to be introduced worldwide (?)which/when?)

Naming mAb: 1) first 2 - 4 letters – WHO/sponsor picks 2) middle part: disease/target e.g. immune –li-; cardiac –ci-; tumor –tu- 3) type of antibody -omab =murine, -ximab = chimeric, -zumab = humanized, -umab = human.
Personalized Medicine: Promise and Pitfalls

For individual patients, this could

- Predict responses to individual drugs
- Predict toxicities to individual drugs
- Optimize benefits / risks of treatment
- Achieve better outcomes
- Reduce costs
Response to TNF-I Therapy: PTPRC gene

- 1,115 UK RA patients on TNF-I therapy
- 29 SNPs established as RA susceptibility variants
- PTPRC rs10919563 SNP associated with improved treatment response; no association with other loci seen
- “meta-analysis combining these data with results from previous study strengthened the evidence (p=5.13 X 10^{-5})”

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Baseline DAS28</th>
<th>Change in DAS28</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/1</td>
<td>6.66 ± 0.95</td>
<td>-2.53 ± 1.51</td>
</tr>
<tr>
<td>1/2</td>
<td>6.73 ± 0.99</td>
<td>-2.32 ± 1.46*</td>
</tr>
<tr>
<td>2/2</td>
<td>6.75 ± 1.00</td>
<td>-2.35 ± 1.43*</td>
</tr>
</tbody>
</table>

*P 0.04; Plant D, et al. Arthritis Rheum 2012;64:665-70

Personalized medicine: KRAS and other mutations in colorectal and NSCLC

<table>
<thead>
<tr>
<th>Oncogene (prevalence)</th>
<th>Rx Response, NSCLC pts</th>
</tr>
</thead>
<tbody>
<tr>
<td>EGFR (40%) Asian,10% Cau</td>
<td>erlotinib: ~ 82% gefitinib: ~ 72%</td>
</tr>
<tr>
<td>KRAS</td>
<td>a-EGFR ~0-5%</td>
</tr>
<tr>
<td>ALK</td>
<td>crizotinib ~55%</td>
</tr>
</tbody>
</table>

FDA approves Therascreen KRAS PCR Kit (Qiagen). [www.cancer.gov](http://www.cancer.gov) July 6, 2012. New test for 280 (Foundation Medicine) different genetic mutations ($5,800); "~ 70% cases mutation targeted by an approved or in-trial drug’


>3 X 10^9 measurements, 20 time points over 14 months, single pt (Michael Snyder, PI)

**Clinical Responses to TNF Inhibitors**

Serum Levels of ADA Correlate With Antidrug Antibody Levels


Rapid reversal of pain induced BOLD signals after TNFi on fMRI in RA

Hess A. PNAS (Epub Feb 2011)
Biosimilar (CT-P13) vs IFX in MTX-IR RA and in AS: Two studies

- 606 RA patients
  - 1:1 IFX (n=304) vs CT-P13 (n=302)
  - 3 mg/kg + MTX at Weeks 0, 2, 6, 14, 22, 30
  - 1º outcome ACR20 at Week 30

<table>
<thead>
<tr>
<th></th>
<th>CT-P13</th>
<th>IFX</th>
</tr>
</thead>
<tbody>
<tr>
<td>AE (%)</td>
<td>35.2%</td>
<td>35.9%</td>
</tr>
<tr>
<td>Infection AE (%)</td>
<td>15.3%</td>
<td>16.9%</td>
</tr>
<tr>
<td>Infusion Rx (%)</td>
<td>5%</td>
<td>6%</td>
</tr>
<tr>
<td>TB (n)</td>
<td>3</td>
<td>1</td>
</tr>
</tbody>
</table>

- 250 AS patients:
  - 5 mg/kg at wks 0, 2, 6, 14, 22, 30
  - 1º outcome: PK (AUC/C\text{max}) similar
  - ASAS20: 70.5% vs 72.4% IFX
  - ASAS40: 51.8% vs 47.4% IFX

CT-P13 has efficacy, safety and PK similar to IFX in MTX-IR RA patients and in AS patients

Yoo DH, et al. EULAR 2012, Berlin, #FRI0143;
Park W, et al bid OP0167

RA – emerging and future therapies
Early Synovial Histopathology

Fibroblast
Myeloid
Lymphoid

IL-1, TNFα, IL-6 (sIL-6R)

Macrophage
Dendritic cell

T-cell
B-cell

Cytokine Interplay

Bone & Cartilage

IL-1, TNFα
IL-6

IL-11, IL-10, IL-12, IL-27, IL-32,
OSM GM-CSF, M-CSF, IFNγ,
PFGF, RANKL, TGFβ

IL-1, TNFα
IL-6

IL-2, IL-4, IL-7 IL-9, IL-10, IL-12 IL-13 IL-15, IL-21, IL-23, IL-27, IFNγ,
TGFβ

## Novel Immunomodulatory Targets

<table>
<thead>
<tr>
<th>Class</th>
<th>Mechanisms</th>
<th>Examples of targets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-cytokines/Growth factors</td>
<td>Anti-cytokine biologics</td>
<td>TNFα, IL-1β, IL-7, IL-12, IL-15, IL-1, 7, IL-18, IL-23, IL-6, IL-32, etc</td>
</tr>
<tr>
<td></td>
<td>p38 pathway</td>
<td>p38</td>
</tr>
<tr>
<td></td>
<td>NF-κB pathway</td>
<td>NF-κB pathway (IKKα, IKKβ, MEKK-3)</td>
</tr>
<tr>
<td></td>
<td>ERK pathway</td>
<td>ERK, COT</td>
</tr>
<tr>
<td></td>
<td>Proteasens</td>
<td>ICE, TACE, TRRE</td>
</tr>
<tr>
<td></td>
<td>Ion channels</td>
<td>P2X7</td>
</tr>
<tr>
<td></td>
<td>Angiogenesis</td>
<td>VEGF, Tubulin, Angio/Endostatin, Tie-2, αvβ3, PAR-2, SCL-2, p53</td>
</tr>
<tr>
<td></td>
<td>Synoviocyte apoptosis</td>
<td></td>
</tr>
<tr>
<td>Anti-Cell trafficking</td>
<td>Leukocyte recruitment</td>
<td>CCR-1, CCR-2, C5a receptor, LTαβ, CCR-2, MIF, Integrins, selectins, ICAMs</td>
</tr>
<tr>
<td></td>
<td>Anti-chemoattractants</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Adhesion molecules</td>
<td></td>
</tr>
<tr>
<td>Anti-B-cells</td>
<td>B-cell biologics</td>
<td>CD-20, CD-19, CD40, IL-6, BAFF/BLYS, APRIL, BTK, NIK, SYK</td>
</tr>
<tr>
<td></td>
<td>B-cell signaling</td>
<td>CCR-5</td>
</tr>
<tr>
<td></td>
<td>B-cell recruitment</td>
<td></td>
</tr>
<tr>
<td>Anti-T cell/co-stimulation</td>
<td>Co-stimulation</td>
<td>B7 (CTLA-4 Ig), CD40L, CD-24, Cat S, GILT, PKCα, LCK, TIRC-7, FK506BP, IFN, JAK-3</td>
</tr>
<tr>
<td></td>
<td>Antigen presentation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>T-cell activation</td>
<td>DHODH, DHFR</td>
</tr>
<tr>
<td></td>
<td>TH-1 / TH-2 / TH-17 / T-Reg balance</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Th Cell Development

![Th Cell Development Diagram](image)

Brodalumab (anti-IL-17R IgG2 mAb): Phase 2 study in MTX-IR patients

- DBPCRCT in 252 MTX-IR patients
- PBO, 70, 140 or 210 mg SC Day 1 and Wks 1, 2 and q2w thereafter
- 1° EP: ACR50 at Week 12
- ACR50: Subset analyses unrevealing
- Despite impressive efficacy in psoriasis, no evidence of benefit or change in CRP in RA

To date, 3 anti IL-17 mAbs have not shown impressive efficacy in RA
**Classical cytokine regulated responses**

- **Proliferation**
- **Differentiation**
- **Gene expression**
- **Survival**
- **Death**

**Inhibitors**

- **Anakinra**
- **Ixeixizumab**
- **Secukinumab**

- **Interleukin**
- **TNF family**
- **TLR agonist**

- **Interleukin**
- **Interferon**
- **Growth factor**

**Inhibition**

1. Anti-TNF antibody
2. Inhibitors of transcription or translation; modulation of mRNA
3. Inhibitory peptides or peptido-mimetics
4. Soluble TNFr1 or TNFr2 constructs
5. Inhibition
6. Inhibitors of downstream signal transduction
7. Factors increasing secretion of soluble forms of TNFr1 and TNFr2

**Cell Surface**

- TNF converting enzyme

**Nucleus**

- DNA
- RNA

**Factors**

- Inhibitors of transcription or translation; modulation of mRNA
- Inhibitory peptides or peptido-mimetics
- Soluble TNFr1 or TNFr2 constructs
- Inhibition
- Inhibitors of downstream signal transduction
- Factors increasing secretion of soluble forms of TNFr1 and TNFr2
Intracellular Signaling Pathways / Molecules

Janus Kinases (JAK) family

<table>
<thead>
<tr>
<th>Cytokine receptors sharing the γc chain</th>
<th>Homodimeric cytokine receptors</th>
<th>Cytokine receptors sharing IL-1R/IL-1 subunit</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-2</td>
<td>IL-6</td>
<td>Erythropoietin</td>
</tr>
<tr>
<td>IL-12, IL-23</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>JAK1 inhibitor</th>
<th>JAK2 inhibitor</th>
<th>JAK3 inhibitor</th>
<th>Tyk2 inhibitor</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>
Cytokine regulation of JAK family members and small molecule targeted interventions

<table>
<thead>
<tr>
<th>JAK Family</th>
<th>Cytokine</th>
<th>Small Molecule inhibitor</th>
</tr>
</thead>
<tbody>
<tr>
<td>JAK-1</td>
<td>IL-2, IL-4, IL-7, IL-9, IL-13, IL-15, IL-21, IL-6, IL-11, IL-27, LIF, OSM, CNTF, CT1, Leptin, IL-10, IL-19, IL-20, IL-22, (IL-24, IL-26) IFNα, IFNβ, IFNγ, IL-28, IL-29, IL-30 (type-III IFN)</td>
<td>Tofacitinib</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ruxolitinib</td>
</tr>
<tr>
<td></td>
<td></td>
<td>INCB-28050</td>
</tr>
<tr>
<td></td>
<td></td>
<td>GLPG-0634</td>
</tr>
<tr>
<td>JAK-2</td>
<td>IL-3, IL-5, GM-CSF, IL-6, IL-11, IL-27, LIF, OSM, CNTF, CT1, CLC, IL-12, IL-23 EPO, GH, PRL, Leptin</td>
<td>Tofacitinib</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ruxolitinib</td>
</tr>
<tr>
<td></td>
<td></td>
<td>INCB-28050</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AC-430</td>
</tr>
<tr>
<td>JAK-3</td>
<td>IL-2, IL-4, IL-7, IL-9, IL-13, IL-15, IL-21</td>
<td>Tofacitinib</td>
</tr>
<tr>
<td></td>
<td></td>
<td>VX-509</td>
</tr>
<tr>
<td></td>
<td></td>
<td>R-348</td>
</tr>
<tr>
<td>TYK-2</td>
<td>IL-6, IL-11, IL-27, LIF, OSM, CNTF, CT1, CLC, IL-12, IL-23 IFNα, IFNβ, IFNγ, IL-28, IL-29, IL-30 (type-III IFN) Leptin</td>
<td>--</td>
</tr>
</tbody>
</table>

Baricitinib, Oral JAK 1/2 inhibitor: 12-week Phase 2b dose-ranging study in MTX-IR (Lilly/Incyte)

**ACR Responses at Week 12**

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>1 mg QD</th>
<th>2 mg QD</th>
<th>4 mg QD</th>
<th>8 mg QD</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACR20</td>
<td>41</td>
<td>57*</td>
<td>75*</td>
<td>78*</td>
<td></td>
</tr>
<tr>
<td>ACR50</td>
<td>10</td>
<td>31*</td>
<td>35*</td>
<td>40*</td>
<td></td>
</tr>
<tr>
<td>ACR70</td>
<td>2</td>
<td>12*</td>
<td>8</td>
<td>23*</td>
<td>20*</td>
</tr>
</tbody>
</table>

Statistical significance w/ 1, 4, 8 mg all p<0.001 vs PBO

**ACR Responses at Week 24**

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>1 mg QD</th>
<th>2 mg QD</th>
<th>4 mg QD</th>
<th>8 mg QD</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACR20</td>
<td>63</td>
<td>78</td>
<td>73</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACR50</td>
<td>48</td>
<td>55</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACR70</td>
<td>20</td>
<td>28</td>
<td>24</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Statistical significance w/ 1, 4, 8 mg by 1° EP at Wk 12; Clinical benefit at 12 weeks sustained with further improvement.
Treat to target algorithm

- **Main target**: Active RA
  - Assess disease activity about every 3 to 6 months
  - Use a composite measure of disease activity every 1 to 3 months
  - Adapt therapy according to disease activity
  - Adapt therapy if state is lost

- **Alternative target**: Low Disease Activity
  - Assess disease activity about every 3 to 6 months
  - Adapt therapy according to disease activity
  - Adapt therapy if state is lost

**PRESERVE: Established RA, can TNFi be lowered or discontinued?**

- 604 RA pts w/ moderate RA (DAS28 3.2–5.1) on ETN/MTX x 9 mos → LDAS
- DBRCT: 1) Continue E50/MTX; 2) Reduce E25/MTX; 3) Placebo/MTX

<table>
<thead>
<tr>
<th>Period 2 Arm</th>
<th>Week 88 outcomes</th>
<th>Rem</th>
<th>mTSS</th>
</tr>
</thead>
<tbody>
<tr>
<td>E50/M (continue)</td>
<td>82.6</td>
<td>66.7</td>
<td>-0.06*</td>
</tr>
<tr>
<td>E25/M (Reduce)</td>
<td>79.1</td>
<td>60.2</td>
<td>+0.5</td>
</tr>
<tr>
<td>P/M (MTX w/d)</td>
<td>42.6</td>
<td>29.4</td>
<td>+0.6*</td>
</tr>
</tbody>
</table>

**P<0.001 vs P/M; *P<0.05 vs P/M**

- No differences in SAE: 2 deaths in E50/M
- SIE = 6; Malignancies = 7; TB = 0

**Time to loss of LDAS & DASΔ >0.6**

- Kaplan-Meier survival estimates (%)
- **ETN 50 mg + MTX**
- **ETN 25 mg + MTX**
- **PBO + MTX**

In P2: mITT, observed cases. P<0.0001, ETN 50 mg/25 mg + MTX vs PBO +MTX, from log rank test

**After 9 mo induction of LDAS with MTX/ETN, pts can safely continue or ↓ ETN dosing; maintenance on MTX alone insufficient to maintain LDAS**

T2T strategies in early RA: OPTIMA Study design


- MTX-naive pts ≥18 ys with RA <1 y & active disease (DAS28>3.2, ESR ≥28 mm/h or CRP ≥1.5 mg/dL), and either >1 erosions, RF+ or anti-CCP+

* n=207 (44.4%)

MTX titrated to 20 mg/wk by Wk 8

* Period 1 DAS28 <3.2 (LDA) at BOTH weeks 22 AND 26

For many early RA patients in LDA on TNFi/MTX, TNFi can be withdrawn for a year; some patients may need continued treatment

The Benefit / Risk Balance

**Benefit**
- Signs / symptoms
- Quality of life / function
- Prevent X-ray damage
- Work / home productivity
- Cost-efficacy

**Risk**
- Infection
- Malignancy
- Other adverse events
- Cost

Patient demographics
- Comorbidity
- Disease characteristics
- Other medications

Rheumatoid Arthritis: New and Emerging Agents and Trends

Arthur Kavanaugh, MD
Director, Center for Innovative Therapy
Professor of Medicine
Division of Rheumatology, Allergy, and Immunology
University of California San Diego
San Diego, CA