Update on Biologics and Targeted Therapeutics in Rheumatologic Disease
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Learning Objectives

• What have we learned about biologics and targeted therapies?

• What about these meds will make your patient’s day?

• What about these meds will ruin your patient’s day (and yours)? What do I need to be vigilant about?
Disclosures/Off Label Use

Consultant:

AbbVie, Amgen, BMS, Pfizer, Roche,

Clinical Trials & Research Grants:
AbbVie, Amgen, Gilead, Pfizer, Sun Pharma

No off label use will be discussed except to mention presence of clinical trials addressing these

The speaker is responsible for the content
Disclaimers

• Rheumatoid Arthritis (RA-Centric)
• Emphasis on the therapeutics of tomorrow
• Non-RA biologics NOT covered
  — Antibody mediated antagonism of IL-17, IL12/23, BAFF, used in PsA, AS, SLE
  — Indirect consideration of agents for other diseases (e.g. anti-IL6 in GCA, RTX in AAV)
Outline:

- RA Overview
- RA Therapy
- JAK Inhibitors
- Safety
Rheumatoid Arthritis

Articular Disease:
Presentation (women>men 4:1)
Synovial inflammation
Seropositive and Seronegative
Strong HLA-DR linkage
Difference Between Normal Joint and Joint Affected by RA

Normal Joint

Joint Affected by RA

Muscle
Cartilage
Tendon
Bone
Synovium
Synovial Fluid
Joint Capsule

Bone Loss/Erosion
Cartilage Loss
Inflamed Synovium
Swollen Joint Capsule

Adapted from US Department of Health and Human Services Handout on Health. Publication 04-4179.
Slide courtesy of Peng T Fan, MD.
Myeloid vs Lymphoid
Lymphoid Aggregates, B cells, Ectopic Lymph Nodes
Key Features of RA

Synovitis
- Swelling confined to area of the joint capsule
- Synovial thickening feels like firm sponge
- Early involvement of hands and feet
- Morning stiffness lasts over 30 minutes

Joint Distribution
- Symmetric polyarthritis
- Corresponds to the distribution of synovial lined joints
- Absence of axial involvement except at C1-2

Slide courtesy of Peng T Fan, MD.
Key Features of RA (Continued)

Hand Deformities

Wrist

Slide courtesy of Peng T Fan, MD.
Key Features of RA (Continued)

Foot Deformities

Slide courtesy of Peng T Fan, MD.
Rheumatoid Factor (RF)
- Positive predictive value of 28%
- Positive in 5% of general population
- May be negative in RA
- May be negative early and positive later
- Positive in other diseases
- 15% are persistently RF-negative and tend to have milder disease

Anti-CCP Antibody
- More specific assay than RF
- Sensitivity ~ 66.4%, specificity ~ 98.3% (active TB: 7–39%)
- Present in early and preclinical disease (up to 14 years)
- Correlates with increased risk for progressive joint damage
- Does not correlate with fluctuation of RF
- Anti-CCP antibody may be positive in RF-negative patients

Combination of positive RF and anti-CCP in early RA predicts high risk for persistent RA

Slide courtesy of Peng T Fan, MD.
RA: Seropositive vs Seronegative

Early RA Clinic <6 months Sx
- 50% seropositive
- 50% seronegative
- Cannot tell difference unless nodules, ILD

“Established” RA - 2 years
- 75% seropositive
- 25% seronegative
- Half of seronegatives remit, never to recur

“Refractory” RA
- 85% seropositive
- 15% seronegative

Morbidity, mortality, extra-articular disease in Seropositives >> Seronegatives
Outline:

• RA Overview
• **RA Therapy**
• JAK Inhibitors
• Safety
Targeting Rheumatoid Arthritis

Tolerance broken - AutoAb appear

Adaptive Immunity
- Methotrexate/HCQ
- Leflunomide
- Abatacept
- Rituximab
- JAK inhibitors
- Prednisone

Innate Immunity
- TNF-Inhibitors
- IL-6-inhibitors
- JAK inhibitors
- Prednisone

Joint Targeting

Ineffective inhibitors
- IL-17
- IL12/23
- BAFF
- IL-1

Tissue Injury
RA: Synovial-Systemic Interactions
Where do these drugs work?

Systemic inflammation

Adaptive Immunity
(B/T Cells)
Methotrexate/HCQ
Leflunomide
Abatacept
Rituximab
JAK inhibitors
Prednisone

Joint Inflammation
MΦ, FLS,

Innate Immunity
TNF-Inhibitors
IL-6-inhibitors
JAK inhibitors
Prednisone
RA Therapy - Section 1

A few slides on Methotrexate until 2025 since it is cheap, easy to take, well-tolerated and it works
Methotrexate Response

Remission/Low Disease Activity

LDA (TEAR) 28%
ACR 50 (SWEFOT) 33%
Remission (CATCH) 38% (3 yr)

Long-term data the same
No anti-TNF superior

2. Saevarsdottir S et al. ARD 70: 469 2010
3. Schulman E et al. ACR 2015 #3182
SWEFOT EARLY RA TRIAL: Predictors of MTX Response

ACPA/RF: No effect
Prednisone 10 mg/d or less (OR 2.84)

Saevarsdottir S et al. ARD 70: 469 2010
Registry: Effect of BMI on Response

Canadian Early Arthritis Cohort (CATCH)\(^1\)
1066 patients with early RA 3 year f/u
BMI: 33% had BMI <25
35% had BMI 25-30;
33% had BMI >30

Relative to BMI 18.5-25 the OR of remission
BMI 25-30: 0.75
>30-35: 0.63

1. Schulman E et al ACR 2015 #3182
Only depression and BMI affected SDAI remission rates in multivariate analysis.


Depression as risk factor for non-response
RA Therapy-Section 2

What to do after an inadequate response to MTX?
Myeloid vs Lymphoid
Lymphoid Aggregates, B cells, Ectopic Lymph Nodes
Let’s Pretend We Can Compare Across MTX-IR Clinical Trials In RA at 12-24 weeks

Bari: 51%
Upa: 45%

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Response (%)</th>
<th>N</th>
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<tbody>
<tr>
<td>Adalimumab (+ MTX)</td>
<td>39%</td>
<td>207</td>
</tr>
<tr>
<td>Infliximab (+ MTX)</td>
<td>31%</td>
<td>87</td>
</tr>
<tr>
<td>Etanercept (+ MTX)</td>
<td>39%</td>
<td>59</td>
</tr>
<tr>
<td>Tocilizumab (+ MTX)</td>
<td>32%</td>
<td>398</td>
</tr>
<tr>
<td>Abatacept (+ MTX)</td>
<td>40%</td>
<td>424</td>
</tr>
<tr>
<td>Rituximab (+ MTX)</td>
<td>26%</td>
<td>170</td>
</tr>
<tr>
<td>Tofacitinib (+ MTX)</td>
<td>32%</td>
<td>321</td>
</tr>
<tr>
<td>Triple Therapy (+ MTX + HQ + SSZ)*</td>
<td>20%</td>
<td>81</td>
</tr>
</tbody>
</table>

* MTX=20 mg qw, HCQ=200 mg BID, SSZ=500-1000 mg BID
1-7. USPI, 2018; 8. Moreland, 2012
SELECT-COMPARE: MTX-IR at Week 12
Adalimumab vs. Upadacitinib

Patients (%)

14.9 13.8
45.2 45.0
29.1 28.7

ACR50

DAS28-CRP ≤3.2

PBO (n=651)  UPA 15 mg QD (n=651)  ADA 40 mg EOW (n=327)

Full analysis set
Non responder imputation
***p<0.001, UPA versus PBO
RA-BEAM: Baricitinib superior to ADA

BARI vs ADA

ACR20 Response

Primary Endpoint

Placebo
Baricitinib
Adalimumab

***$P<0.001$ baricitinib vs placebo or adalimumab; $^+P<0.05$, $^{++}P<0.01$, $^{+++}P<0.001$ baricitinib vs adalimumab.
Secondary endpoint: baricitinib versus adalimumab at 12 weeks (70% vs. 61%, $P = 0.014$).

RA Therapy-Section 3

What to do after an inadequate response to a TNF antagonist?

RCT parity between biologics

The more biologics you fail the less likely you will respond
Baricitinib in Biologic-IR RA
Mean disease duration 14 years

TNF IR

ACR20 response

Primary endpoint

*P ≤ 0.05, **P ≤ 0.01, ***P ≤ 0.001 for supportive analyses comparing baricitinib with placebo, without adjustment for multiple comparisons. †P ≤ 0.001 for comparisons between baricitinib at the 4-mg dose and placebo for the end points of the ACR20 response at week 12, in an analysis that was strongly controlled for multiple comparisons.

Outline:

- RA Overview
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‘Just another kinase’ 1 & 2
Janus associated kinase
Jaks and Signaling by Type I/II Cytokine Receptors

γc family
IL-2 etc

INF-γ

IL-6 family

IL-12, IL-23

Hormone,
Epo,
GM-CSF

Tofa  +  +  +  +  +
Bari  +  +  +  +
Upa   +  +
Filgo +  +  +
JAK inhibitor efficacy in RCT

- RA, PsA, AS, GCA, PMR
- Eczema, alopecia areata, psoriasis
- Ulcerative Colitis, Crohn's
- What’s next?
  - Soft tissue pain, Fatigue, Bursitis?
Outline:

- RA Overview
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- JAK Inhibitors
- Safety
Safety issues rise and fall

Serious Infection rates with biologics HR 1.5-2

Some studies no difference at all-why?

......the power of tapering prednisone
Estimated incidences of serious infections in 100 patients per year by treatment and risk profile.


Risk Factors: >60, COPD, CRF, Infection, Functional Status
Safety issues rise and fall

Topics of interest
Prednisone >10 mg/d
ASCVD
Zoster
Thrombophilia
RA $\rightarrow$ CV Mortality Disappeared?

- 1980-9
- 1990-9
- 2000-7

RA and Non-RA mortality trends over years since RA diagnosis and index date.
Safety issues rise and fall

Topics of interest

Prednisone >10 mg/d
ASCVD
Zoster
Thrombophilia
Herpes Zoster Rates in Tofacitinib vs Other Biologics

To date, a class effect

WGET 4.5/100 pt-yrs

WGET = Wegener’s Granulomatosis Etanercept Trial.

Tofacitinib for Treatment of Rheumatoid Arthritis (NDA 203214) Advisory Meeting.
2017 knowledge about jakinibs:

Safety not likely to be an issue\(^1\)

- 6194 patients on tofacitinib (19,406 patient-years)

IR serious infections: 2.7/100 pt-yrs
IR herpes zoster: 3.9/100 pt-yrs
IR for GI perforations: 0.1/100 pt-years

SIR for malignancy: <1

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“........the study showed the overall incidence of pulmonary embolism to be 5-fold higher in the tofacitinib 10mg twice daily arm of the study compared with the [tumor necrosis factor] TNF inhibitor arm, and approximately 3-fold higher than tofacitinib in other studies across the tofacitinib program,” European Medicines Agency says.

“all-cause mortality in the 10mg twice daily arm in the study was higher than in the 5mg twice daily and TNF-I arms.”
VTE and Jakinibs:

• Class Effect re thrombophilia?
  • Filgotinib yet to be besmirched
• If real, mechanism?
  • Rofecoxib or Celecoxib or Troglitazone?
Rare and not so rate events

Rarer events:
IL6 inhibition and diverticular perfs 3/1000 ~HR 2
RTX and PML (1:40,000 patient years)
TNF-I and MS: 1:10,000 patient years
TNF-I and ILD: increased death from ILD

Diabetes and NASH: Hepatotoxicity of MTX, TCZ
Learning Objectives

• What have we learned about biologics and targeted therapies?
  – Highly effective agents exist
  – Cost the biggest barrier until 2025?
What about these meds will make your patient’s day?

The need for these agents is well-defined

Efficacy measures and predictors are clear

Lifestyle (weight loss, tobacco cessation) provide clear yields
Learning Objectives

• What about these meds will ruin your patient’s day (and yours)? What do I need to be vigilant about?
  – Prednisone dose
  – Recurrent infection typically sinopulmonary
  – Rare side effects
  – Efficacy of Zoster vaccination studies
Thank you! Questions?
Does Seropositivity Predict Outcomes?

No evidence for differential with ETN/INF$^{1,2}$

RF Differential: **Rituximab (OR 5.0)**

TCZ OR increased by RF 1.5X not ACPA$^{3-5}$

No data: **Tofacitinib**

Four Questions in RA Pathophysiology

What to do with a seropositive individual without symptoms, mild symptoms, or intermittent symptoms (e.g., PR) and no findings?

How does systemic autoimmunity (ACPA) become synovial autoimmunity?

When does it become RA?

How is RA related to lung and cardiovascular comorbidities?

PR = palindromic rheumatism
Polling Question

You have a patient with positive ACPA without symptoms.

What is the likelihood of RA in 3 years?

A. <5%
B. <10%
C. <20%
D. <30%
E. <50%
F. >60%
The Likelihood of RA with Positive ACPA Results

Diagnostic Accuracy of ACPA in the General Population

• Serum from Swedish twin cohort (n = 12,590)
• 350 of 12,590 individuals had positive anti-CCP2 test
• 103 had RA diagnosis at blood donation (29.4%)
• 21/247 (8.5%) developed RA in over 3 years

Diagnostic Accuracy of ACPA in Patients with Lung Disease

• 33 high titer ACPA positive patients w/ILD
• 3 (9%) → RA with median follow up 449 days

You are seeing a 35-year-old woman with ACPA and/or RF+ with peri-menstrual arthralgias. What is the likelihood of RA in 1 year?

A. <5%
B. <10%
C. <20%
D. <30%
E. <50%
F. >60%
147 seropositive patients with arthralgia. 50 ACPA, 52 RF, 45 double positive:

- 29/147 (20%) $\rightarrow$ polyarthritis in over 28 months
- 26/95 (ACPA+ACPA/RF) = $\sim27\%$ (<14%/year)
- 26/29 who progressed were ACPA+ = 90%
- 3/52 (6%) with isolated RF $\sim<$3%/year