Rheumatoid Arthritis
Treatment Past, Present and Future

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Conclusion
A new era in the treatment of rheumatoid arthritis

- Proof of principle has been established that selective targeting of pathogenic elements is therapeutically effective.
- Early therapy—especially combination therapy tied to improved outcomes.
- The future is now! Less joint replacements and improved morbidity and mortality now evident.
- Biologics decrease joint replacements and hospitalizations
- A plea. Refer to confirm diagnosis and initiate treatment

The Characteristics of RA
Systemic chronic inflammatory disease
- Mainly affects synovial joints
- Variable expression
- Risk increased by both genetic and environmental factors
- Strongest genetic risk conferred by shared epitope in close association with class II MHC gene, (HLA) DR4
- Cigarette smoking clearly an environmental trigger

The Characteristics of RA, cont’d
- Prevalence about 1%
- Worldwide distribution
- Female: Male ratio 3:1
- Peak age of onset 25 – 50 years
- Synovitis, but tends to spare the LS spine

The Rapid Pace of Drug “Discovery” in Rheumatology

<table>
<thead>
<tr>
<th>Year Marketed for RA</th>
<th>1995</th>
<th>2000</th>
<th>2006-2010</th>
<th>2013</th>
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<td>CsA</td>
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<td>Rituximab/abatacept</td>
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<td>Tocilizumab</td>
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Disclosures
CVS
ACR Criteria for Diagnosis

- Four or more of the following criteria must be present:
  - Morning stiffness > 1 hour
  - Arthritis of ≥ 3 joint areas
  - Arthritis of hand joints (MCPs, PIPs, wrists)
  - Symmetric swelling
  - Serum rheumatoid factor
  - Radiographic changes
- First 4 must be present for > 6 weeks

New 2010 American College of Rheumatology/European League Against Rheumatism Classification Criteria for Rheumatoid Arthritis

<table>
<thead>
<tr>
<th>Description</th>
<th>Score</th>
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<tr>
<td>Morning stiffness &gt; 1 hour</td>
<td>1</td>
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<tr>
<td>Arthritis of ≥ 3 joint areas</td>
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<tr>
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<td>1</td>
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<tr>
<td>Symmetric swelling</td>
<td>1</td>
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<tr>
<td>Serum rheumatoid factor</td>
<td>1</td>
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<td>Radiographic changes</td>
<td>1</td>
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<td>≥ 6 weeks for classification of a patient as having definite RA.</td>
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Who should be tested? Patients with definite clinical synovitis of at least one joint not better explained by another disease process. Score-based algorithm: add scores of A-D; a score of ≥6/10 is needed for classification of a patient as having definite RA.

CAD in RA

- Risk of cardiovascular mortality in patients with RA: a meta-analysis of observational studies
  - Avina-Zubieta et al
  - Arth Rheum 2008;59(12):1690

24 studies/111,758 patients—50% increased risk of CVD deaths in RA

Effect of methotrexate

- 5626 RA patients for 25 years
- 666(12%) mortality
- Mtx use >1year associated with lower risk of mortality
- Mtx use -70% reduction in mortality in RA
- Wasko et al. ArthRheum: 65(2) Feb 2013, 334-342

CAD prevention and rheumatology

- Low dose colchicine for secondary preventions of cardiovascular disease JACC 2013;61:404-410 not double blinded study-but decreased risk of ACS by 67%
- CIRT(Cardiovascular inflammation reduction trial) under way—mtx + traditional therapy in stable post-MI patients with type-2 DM/Met Syn
- CANTOS trial—Canukinumab + traditional therapy—prior MI patients with increased crp>2.0 to decrease risk of mi/stroke
The Importance of Early Diagnosis and Treatment

- RA is progressive, not benign
- Structural damage/disability occurs within first 2 to 3 years of disease
- Slower progression of disease linked to early and aggressive treatment
- Less NSAIDS and steroids
- Less Orthopedic surgery and hospitalizations

Advantages of DMARDs

- Slow disease progression
- Improve functional disability
- Decrease pain
- Interfere with inflammatory process
- Retard development of joint erosions
- Remissions are now achieved
- Most studies correlate favorable outcomes with combination Rx or early and aggressive therapy

ACR Treatment Algorithm

Establish diagnosis of RA early
Initiate therapy
Periodically assess disease activity
Adequate response
Inadequate response
Change/add DMARDs
Suboptimal MTX response
MTX naïve
MTX Other Combination
MTX Other monotherapy
MTX Other Combination
MTX Other monotherapy
MTX Other Combination
Multiple DMARD failure
Symptomatic and/or structural joint damage

Methotrexate

- Very effective
- In use over 50 years
- First double blind study published 1985 NEJM
- Documented to change natural history, decrease extra-articular manifestations including possible cardiac disease and increase QOL and survival
- The standard of care
- Newer data shows significant mortality reduction if on methotrexate > 1 year

Dosing - MTX

Weekly
Oral - One Dose
- Cycled
Initial Dose
7.5 mg/wk
Therapeutic
Unknown (7.5 – 25 mg/wk) - now recognized effective dose = 10mg/m2
Always with folic acid or folinic acid
Maximum
25 mg/wk/other ways to deliver and make "more tolerable" (sc, folinic acid)
Maintenance
Lowest dose possible
Steroid reduction


NEJM Volume 312:818-822 March 28, 1985 Number 13

Efficacy of low-dose methotrexate in rheumatoid arthritis

ME Weinblatt, JS Coblyn, DA Fox, PA Fraser, DE Holdsworth, DN Glass, and DE Trentham
Methotrexate

- Efficacy—Now established DMARD
- Patients with RA—treated with mtx decreased mortality and c/v risk—Other studies confirmed these observations
- Established Gold Standard

Next therapy after Methotrexate: How to decide when and what

- Disease activity—Use objective measurements—DAS, CDAI
- Radiographic progression
- Patient’s appetite for risk
- Prior medical issues which may make some therapies contraindicated
- Economic review of systems!
- Triple small molecule therapy/leflunomide +/- MTX
- And how to decide next drug?

Biologic Therapies

- Changed the face of RA
- Induce remission
- Change the natural history even without a clinical improvement!
- Adverse events but no “new signals”
- Early use in methotrexate “inadequate responders”
- But methotrexate is great in 20-30% if used correctly

Biologic Therapies as of 2013

- Five anti-tnf agents—etanercept, adalimumab, infliximab, golimumab and certolizumab pegol
- IL1-receptor antagonist—anakinra
- Co-stimulatory blocker—abatacept
- B cell depletion—rituximab
- IL6 receptor antagonist—tocilizumab

Anti-Tnf Therapy

- All have similar effects—with roughly a response rate of 60-70%
- Work in early disease and late disease—clinical outcomes better in early disease
- Stabilize radiographic progression
- Decreased NSAIDS, steroids and mtx doses
- Remission in some studies upon withdrawal

“Try this—I just bought a hundred barbs.”
**Absolute contraindications to TNF-Blockers**

- CHF III/IV
- Active/latent Tb
- Active infection
- Active or recent h/o malignancy (solid tumors)
- MS/optic neuritis
- h/o lymphoma
- Live vaccines
- Anaphylaxis

Adapted Semin A&R 2005;34

**Newer Biologics in RA**

- Abatacept
- Rituximab
- Tocilizumab

How many anti-TNFs should we try? Which one to select?? Use these first? Difference in side effects

**Abatacept (CTLA4Ig):**

Interrupts Autoimmune Response Underlying RA

**Mechanism of Action**

CTLA4Ig Blocks Activation

**Abatacept (CTLA4Ig):**

- Normal Activation
- CTLA4Ig Blocks Activation

**Abatacept (CTLA4Ig):**

- **CTLA4Ig** Blocks
- **Activation**

**Tocilizumab**

- Humanized mAb
- IgG1
- (MW ~150 kd)
- Key Features:
  - Binds soluble and membrane bound IL-6R
  - Weak/no CDC* or ADCC** effector functions (in vivo)

**Tocilizumab**

- Monoclonal antibody that blocks IL6r
- 50% response rate in TNF failures
- Onset 2-12 weeks
- Impressive improvements in CRP, QOL, fatigue
- Toxicity: Infections, GI perforation, lipid, leukocyte and liver test abnormalities.

**Rituximab**

- B cell depletion
- Works about 50% in tnf failures
- Onset 6-12 weeks-may have long term effect
- 2 infusions—1000mg vs 500mg
- Toxicity
Concerns regarding rituximab

- What studies should be done before?
- What order should we add these medicines?
- Can (should) we treat seronegative patients?
- What dosing and intervals and how often?
- How much steroids to use?
- Can we use without methotrexate or with other small molecules?
- When can we add another therapy?
- Will there be more surprising side effects? (PML)

Newer drugs in development

- Newer B cell and anti TNF agents
- p38MAP kinase inhibitors
- Janus Kinase 3 inhibitors-tofacitinib-FDA advisory board approval
- Spleen tyrosine kinase inhibitors
- CCR1 antagonists
- Gene therapy

BRASS
BRIIGHAM AND WOMEN'S HOSPITAL
RHEUMATOID ARTHRITIS SEQUENTIAL STUDY

- Longitudinal prospective cohort of over 1300 RA patients
- Yearly evaluation for disease activity, medication changes, and functional disability
- Questionnaire assessing medication changes and functional disability mailed in-between annual visits
- Started in 2003 and still actively enrolling

Average DAS28-crp

Cost of Care
Oct '11-March '12

Medication Usage
Based on the primary ICD9 diagnosis code, the following diagnoses were observed at PHS:
- Rheumatoid Arthritis 71%
- Psoriatic Arthropathy 6.5%
- Ankylosing Spondylitis 3%
- Iridocyclitis 1%
- Giant Cell Arthritis 1.1%
- Takayasu Disease 0.3%
- Behcets Syndrome 0.3%
- Juvenile Rheumatoid Arthritis 0.5%
- Sarcoidosis 1.5%

11% of patients had diagnoses in more than one of the above categories. 1.3% of patients have “other” diagnosis codes.

Specialty Drug Utilization & Pricing

Summary: Recommendations For Approval

Tofacitinib in RA
- Approved Nov 2012 as Xeljanz
- Not approved in Europe
- Indication- Active RA, inadequate response or intolerance to MTX
- Monotherapy or combo
- 5 mg bid dose approved
- Black Box on infections and malignancy
- Monitoring- CBC, lymphocytes, lipids 4-8 wks after dosing and CBC every 3 months, LFTs
- Cost- approx $ 23000

JAK inhibitors-potential complications
- Infections
  - Opportunistic infections
  - Zoster
- Lipid abnormalities
- Neutropenia
- Anemia
- Increase serum creatinine –
  - clinical significance?
- LFTs
- Malignancy

JAK inhibitors-Questions
- Is there a differential response between monotherapy and combination with mtx?
  - if so what is the mechanism?
- What about lab toxicities- is this class or drug specific
  - Anemia- who develops this
  - Creatinine- what does this mean?
  - Liver blood tests-meaning?
  - Lipids- is the increase pathogenic?
- What about long term infection and malignancy risk—caveats: serious infections same as biologics; 12 cases of B+pop+Hungal-7 Hep b and c;zoster markedly increased-5%
ip avoid in diverticulitis
- What about pregnancy and conception?
- Where will it be positioned and where will it be used?
- Will more selective JAK inhibitors be as effective and offer a toxicity advantage?
Syk inhibitors

An inhibitor of the spleen tyrosine kinase pathway has demonstrated efficacy in Phase 2 studies.
The drug worked quickly achieving response as early as one week in combination with MTX.
One phase 2 study in pts who failed prior biologics was not positive - this may have been due to
study design and patient selection.
Toxicity included diarrhea and hypertension these AEs were responsive to dose reduction and/or
anti-BP meds.
Phase 3 studies are in progress.

Questions re Syk inhibitors

• Does Fostamatinib work as monotherapy?
• Does Fostamatinib work in TNF failures?
• Can you lower dose and maintain response?
• What about toxicities?
  What about long term infection, HBP and malignancy risk?
  What is the etiology of the HBP—VEGF inhibition?
  Is the mechanism of action due to Syk inhibition or other kinase inhibition?
  Where will it be positioned and where will it be used?
  Will more selective Syk inhibitors be as effective and offer a toxicity advantage?

TEAR Study

• Complicated 4 armed study looking at early RA treated with mtx monotherapy with step up to
triple therapy or mtx at 24 weeks/mtx+etanercept/triple therapy/
• At week24 no difference in immediate therapy groups
• At weeks 48 and 102 no difference in groups
• X-ray outcomes favored etanercepet +mtx by less then 1 TSS
• Moreland et al. ArthRheum 2012 Sep;64:2824

Primary: DAS28 between weeks 48 and 102 after initiation of treatment

Secondary:
  – ACR 20, 50, 70
  – Radiographic progression
  – DAS 28 remission
  – Quality of life
  – D/C lack of efficacy

RA (ACR criteria)
  Disease duration < 3 years
  Active disease ≥ 4 swollen, tender by 28-jt count
  RF or CCP or erosions
  ≥ Poor Prognosis RA
  Limited Prior DMARD exposure
  Stable NSAID
  Oral prednisone allowed (≤10mg/day)
  No serious co-morbid conditions
  No significant renal, liver or hematologic lab abnormalities
  No active infections

At Week 24, subjects in Arms 3 & 4 with
DAS ≥ 3.2 will be stepped-up to additional active medications.
The Relationship between Radiographic Progression and Clinical Outcome

- Total Sharp Score (TSS) progression correlates with HAQ progression
  - 1 TSS $\Delta$ equals $\approx 0.01 \Delta$ in HAQ*
- HAQ progression of .22 results in clinically significant change in function
- Therefore, an increase of TSS of 22 equals a clinically important amount of change

*Smolen et al Ann Rheum Dis 2010;69:1058

Further Projection of TEAR Findings

- Cost to prevent one Sharp point progression = $30,000
- Years to reach clinically significant difference (22 point progression) = 36.6 years
- Cost differential in that time = $660,000 for each patient treated

RACAT: Study Design

- Primary Outcome: **xglyph5T7 DAS28
- Start 24 Weeks
- DAS28 Improved $\geq 1.2$ ?
- Yes
- No
- *Etanercept
- **Etanercept
- SSZ + HCQ
- Open Continuation
- Open Continuation
- 24 Weeks
- 48 Weeks

? Etanercept withdrawal
Smolen et al Lancet 2013 Jan 17.

- Looked at 834 patients with moderate DAS on mtx
- Added 50mg weekly etanercept
- At 36 weeks 604 sustained low disease activity score or remission were randomized to 50mg etanercept/25mg etanercept or placebo
- At week 88-83% 50mg group and 43% placebo group low disease activity; 25mg group 79% low disease activity

Conclusion

A new era in the treatment of rheumatoid arthritis

- Proof of principle has been established that selective targeting of pathogenic elements is therapeutically effective.
- Early therapy especially combination therapy tied to improved outcomes.
- The future is now! Less joint replacements and improved morbidity and mortality now evident.
- Cost remain an issue and if we don’t address others will
- But outcomes extraordinary