Rheumatoid Arthritis, Brief Review of Differential Diagnosis and Initial Treatment

Jonathan S. Coblyn, M.D.
Brigham and Women’s Hospital

Disclosures
CVS

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.
- A plea. Refer to confirm diagnosis and initiate treatment

The Rapid Pace of Drug “Discovery” in Rheumatology

<table>
<thead>
<tr>
<th>Year Marketed for RA</th>
<th>CsA</th>
<th>leflunomide</th>
<th>celecoxib</th>
<th>etanercept</th>
<th>infliximab</th>
<th>adalimumab</th>
<th>tocilizumab (2010)</th>
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<tbody>
<tr>
<td>1995</td>
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<td>2000</td>
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<td>2006-2010</td>
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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
Joint Involvement on Presentation of RA

<table>
<thead>
<tr>
<th>Polyarticular</th>
<th>75%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small joints of hands and feet</td>
<td>60%</td>
</tr>
<tr>
<td>Large joints</td>
<td>30%</td>
</tr>
<tr>
<td>Large and small joints</td>
<td>10%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Monoarticular</th>
<th>25%</th>
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<tbody>
<tr>
<td>Knee</td>
<td>50%</td>
</tr>
<tr>
<td>Shoulder</td>
<td></td>
</tr>
<tr>
<td>Wrist</td>
<td>50%</td>
</tr>
<tr>
<td>Hip</td>
<td></td>
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<tr>
<td>Ankle</td>
<td></td>
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<tr>
<td>Elbow</td>
<td></td>
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</tbody>
</table>

Characteristic Features of Rheumatoid Arthritis, cont’d

<table>
<thead>
<tr>
<th>Articular</th>
<th>Extra-articular</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characteristic distribution patterns:</td>
<td>Vasculitis</td>
</tr>
<tr>
<td>· Symmetric</td>
<td>· Pulmonary involvement</td>
</tr>
<tr>
<td>· Proximal interphalangeal, metacarpophalangeal, radiocarpal joint involvement</td>
<td></td>
</tr>
<tr>
<td>· Wrists, elbows, knees, ankles, shoulders, neck, intertarsals, metatarsophalangeals affected</td>
<td></td>
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</tbody>
</table>

Rheumatoid Arthritis

Laboratory Abnormalities

<table>
<thead>
<tr>
<th>Frequent</th>
<th>Occasional</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>Leukocytosis; leukopenia (Felty's/LGL)</td>
</tr>
<tr>
<td>ESR</td>
<td>Platelets</td>
</tr>
<tr>
<td>RF (+)</td>
<td>ACPA (CCP+)</td>
</tr>
</tbody>
</table>

Hyper (γ) Globulinemia
Inflammatory Synovial Fluid

The Pathology of RA

Serositis

1 – Synovitis
   · Joints
   · Tendon sheaths
   · Bursae

2 – Serositis of pleura and pericardium

Nodules
Vasculitis

Differential Diagnosis of Polyarthritis

Rheumatoid Arthritis
PMR/GCA
Psoriatic Arthritis
Crystal – Gout, Pseudogout
SLE/Vasculitis
Sjogren’s and variants
Any “immune complex” illness
Spondylitic variants
Paraneoplastic
Viral – Parvovirus, HepBAg, HCV, Rubella
Lyme
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

Descriptor

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.

New 2010 American College of Rheumatology/European League Against Rheumatism

Classification Criteria for Rheumatoid Arthritis

<table>
<thead>
<tr>
<th>Descriptor</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Joint involvement (use highest applicable category)</td>
<td></td>
</tr>
<tr>
<td>1 large joint</td>
<td>0</td>
</tr>
<tr>
<td>2–10 large joints</td>
<td>1</td>
</tr>
<tr>
<td>1–3 small joints (with or without large joint involvement)</td>
<td>2</td>
</tr>
<tr>
<td>4–10 small joints (with or without large joint involvement)</td>
<td>3</td>
</tr>
<tr>
<td>&gt;10 joints (at least 1 small joint)</td>
<td>5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>B. Serology (high–positive: ≥ 3x upper limit normal for the test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative RF and negative ACPA</td>
</tr>
<tr>
<td>Low–positive RF or low–positive ACPA</td>
</tr>
<tr>
<td>High–positive RF or high–positive ACPA</td>
</tr>
</tbody>
</table>
C. Acute phase reactants
Normal CRP and ESR
Abnormally elevated CRP or ESR

D. Duration of symptoms
<6 weeks
≥6 weeks

ACPA: anti-citrullinated peptide antibodies; CRP: c-reactive protein; ESR: erythrocyte sedimentation rate; RA: rheumatoid arthritis

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

Systemic Disease Affecting:
- Heart and CAD
- Lungs
- Blood vessels-vasculitis
- Muscles
- Eyes
- Skin
- Diarthrodial joints-"Unusual joints"-cricoarytenoid and C-spine
- Neurologic changes

Pulmonary Manifestations
Pleural Effusions
- Exudates > Transudates
- Can have low PH
- Hallmark is low glucose – Often < 30
Rheumatoid nodules

Pulmonary Manifestations
Interstitial Fibrosis
Bronchiectasis
Pulmonary Hypertension
Vasculitis
Bronchiolitis Obliterans
Cardiac Manifestations

Pericardial Effusions – Up to 1/3 in Sero + Groups
  - Tamponade
  - Constrictive pericarditis
Rheumatoid Nodules – CHB, Valvular Lesions
  - Aortitis
  - Myocarditis
  - Amyloidosis

Neurologic Manifestations

Entrapment Neuropathies –
  Median N. > Ulna N.
Peripheral Neuropathy
  Rheumatoid Nodules
Myopathy and Myositis
  Mononeuritis multiplex
Cervical spine and “brain stem” entrapments

Cervical Spine Disease

C1 – C2 Subluxation – Myelopathy – C2
Can damage sensory nucleus V nerve
Vertebral – Basilar Syndromes
  – drop attacks, cerebellar signs, diplopia
Lower cervical root involvement – C5–6–7
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

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

Are Steroids DMARDS?
AIM 2002:136;1-12
- 2 year randomized trials
- 81 RA pts – no prior DMARDs
- 41—10mg prednisone; 40 placebo
- After 6 months—SSZ added as “rescue” if not adequate response
- 1st 6mo.-steroid group – “more clinical improvement”
- After 6 months-better grip strength/28jt score
- BUT—increased compression fractures, skin fragility and weight gain

Anti-Malarial Drugs
- Efficacy
  - RA SLE, DLE, JRA, Psoriatic
- Toxicity
  - Rash
  - Ocular
  - Gastrointestinal
  - Myopathy, Conduction system and cardiac changes
- Dosage
  - Hydroxychloroquine – 400 mg. – Max. 6.5mg/kg
  - Chloroquine – 250 mg. – Max.
- Ophthalmology Exam – 6 month intervals

Sulfasalazine
- Efficacy in open, randomized studies
- Key component of triple therapy—with hydroxychloroquine and methotrexate
- Toxicity:
  - GI most common
  - Hematologic
  - Hypersensitivity reaction
- Potential Role:
  - Early DMARD
  - Reactive arthritis

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 probably survival
- The standard of care

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
“To do” list prior to MTX use

- LFTs, creatinine, albumin and CBC
- Up to date vaccinations - flu and pneumovax and discuss potential live vaccines
- HCV, HBsAg, HBcAg
- CXR - optional but would do in older patient
- PPD

Methotrexate: Toxicity

**Methotrexate: Toxicity**

- Gastrointestinal
- Stomatitis
- Hematologic - comorbid conditions
- Pulmonary
- Liver
- Reproductive
- Opportunistic infections
- ? Neoplasia
- Nodulosis

MTX: Gastrointestinal

**MTX: Gastrointestinal**

- Nausea
- Anorexia
- Vomiting
- Weight loss
- Diarrhea
- Stomatitis

- Varying frequency and severity
- Generally occurs at the time of administration and for next 2 – 3 days
- Rx: Dose reduction, method of administration
  Folic acid, folinic acid therapy

MTX Toxicity: Hematologic

**MTX Toxicity: Hematologic**

- Leukopenia
- Thrombocytopenia
- Anemia
- Pancytopenia

**Risk Factors:**

- Renal insufficiency
- Folate deficiency – elevated MCV
- Infection
- Concomitant drugs: TMP/Sulfa, Probenecid

**Prevention:**

- Routine lab monitoring
- Supplemental folic acid

**Treatment:**

- Leucovorin

Methotrexate: Pulmonary

**Methotrexate: Pulmonary**

- **Clinical** - Nonproductive cough, fever, dyspnea
- **Dose** - Variable
- **Lab** - Eosinophilia, hypoxemia
- **Radiograph** - Infiltrates

**Pathology** - Interstitial pneumonitis
- Bronchiolitis
- Granuloma

**Treatment** - Steroids
- Supportive care

**Outcome** - Variable

Methotrexate: Pulmonary, cont’d
MTX: Opportunistic Infections

- Case Reports in Rheumatoid Arthritis
- Varying duration and dose of MTX
- Organisms
  - Herpes zoster
    - Localized
    - Disseminated
  - PCP
  - Nocardia
  - Cryptococcus
  - Histoplasmosis
  - Aspergillus

MTX: Opportunistic Infections, cont’d

- No concomitant steroids in several patients
- Normal CBC/differentials observed

MTX: Liver

Survey of Members of ACR

58% responded

Identified 24 cases of serious liver disease

Criteria: Clinical – 17
Biopsy – 7

Mean age: 65 years

MTX: Nodules

- Risk factors: Unknown
- Dose and duration: Variable
- Location: Diffuse – Cutaneous – Feet
  - Visceral
Treatment: Unknown
  - Dose reduction
  - Drug cessation
  - Steroids – Systemic and injection
  - Combination Rx: Plaquenil, Sulfasalazine, CsA

MTX Toxicity: Lymphoma

- NHL – 3 patients
  - Diffuse large cell, B cell
  - Treatment duration > 2 years
  - No Sjogren’s symptoms

J Rheumatol 18: 1741–1743, 1991
19: 1462-1468, 1992

Methotrexate

- Efficacy—Now established DMARD
- Lancet 2002;359:1173 1240
  - consecutive pts with RA—treated with mtx decreased mortality and c/v risk—
  - Other studies confirmed these observations
- Still unclear how much “better” newer therapies are
- Established Gold Standard
Selection of an Initial DMARD: Leflunomide

<table>
<thead>
<tr>
<th>PROS</th>
<th>CONS</th>
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<tbody>
<tr>
<td>• Early onset of action (~4 weeks)</td>
<td>• Toxicities: hepatotoxicity, gastrointestinal, hypertension, ?pulmonary, neuropathy</td>
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<tr>
<td>• Stabilized benefit for long-term use</td>
<td></td>
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<tr>
<td>• Selectively targets autoimmune lymphocytes to reduce untoward AEs</td>
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**Leflunomide**

- Pyrimidine synthesis inhibitor
- Selective for dihydroorotate dehydrogenase
- Metabolized in liver to active metabolite
- Well absorbed orally
- Requires loading dose
- Prolonged half-life (14 d)
- Teratogenic

**Leflunomide Dosing**

- Loading dose –variable– 100 mg x 3 days or qod x 3 or even weekly x 3, but most often start daily dosing at
  20 mg QD
- Dose may be decreased to 10 mg QD if tolerability issues arise

**Adverse Events of Potential Clinical Significance**

- Gastrointestinal Events
- Allergic Reactions
- Infections
- Reversible Alopecia
- Hypertension
- LFTs/Cirrhosis/Death if unmonitored
- Potential teratogenesis – consider avoiding in child bearing age unless document counseling
- Cholestyramine use to decrease half life as decreases enterohepatic circulation

**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!
- And how to decide next drug?

**Biologics in the Treatment of Rheumatoid Arthritis**
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

Cost of Care-Risk and Expense

- Early use in methotrexate “inadequate responders”
- But methotrexate is great in 20–30% if used correctly

Biologic Therapies as of 2012

- 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

Etanercept TEMPO Trial

<table>
<thead>
<tr>
<th>ACR 50 Responses (NRI*)</th>
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<tbody>
<tr>
<td>Percentage of Patients</td>
</tr>
<tr>
<td>2 Weeks</td>
</tr>
<tr>
<td>Methotrexate (n = 228)</td>
</tr>
<tr>
<td>Etanercept (n = 223)</td>
</tr>
<tr>
<td>MTX + Etanercept (n = 231)</td>
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</tbody>
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Anti-TNF Therapies

Adverse Events

- Sepsis, Septic Joints, Pneumococci (Pneumovax)
- Tuberculosis (PPD and treat prior)
- Injection site reactions/diffuse rashes
- Pulmonary symptoms
- Increased risk lymphoma/solid tumors
- Increased risk Class III–IV CHF
- Neurologic–demyelination
- Hematologic–pancytopenia
- Autoimmune diseases–SLE
- ?LFT abnormalities
**Tb screening**
- 5mm positive, not 10
- If pos, CXR to r/o active infection
- What if negative, but radiographic stigmata of prior Tb, including calcified granuloma?
- INH 300mg qd 9 months or alternative regimens if from country with drug resistant Tb
- I've had BCG—what to do?
- What about quantiferon—gold?
- How long to wait before initiate anti-tnf?

**TB in setting of anti-TNF**
- Incidence increased fourfold
- 57% developed extrapulmonary tb and increased mortality (15%) 17 miliary others including bone, genital, bladder 25% developed disseminated disease
- Often difficult to diagnose. Biopsies often needed and granuloma often NOT found
- Less often associated with etanercept
- Time to development shorter with infliximab vs etanercept; 48/70 developed Tb after 3 or fewer injections

**Preventive Measures**
- Pneumovax
- How often?
- High index of suspicion even if vaccinated
- ?Pcn prophylaxis in high risk patients

**Anti-TNF and Demyelinating Syndromes**
- 19 patients developed demyelinating syndromes 17 on etanercept
- Paresthesias (13), optic neuritis (8), confusion (5), gait disturbance, facial palsy apraxia
- Four/20 prior MS history
- Most responded partially or completely to withdrawal
- A&R 44:2862, 2001

**Lymphoma**
- Med Watch data
- 26 cases ~18 w/ etanercept and 8 infliximab
- 81% non Hodgkin's lymphomas
- Median interval from therapy to lymphoma development~ 8 weeks
- 2 individuals treated with anti–tnf while lymphoma in remission relapsed and died
- Spontaneous regression in 2 cases
- Arth Rheum 46:2002;3151

**? Increased Risk of Solid Tumors**
- Meta–analysis of multiple studies JAMA 2006;295:2275–85
- Malignancy risk 0.8% compared to placebo +/– Mtx of 0.2% (0.5% if exclude nonmelanoma skin cancers)
- Etanercept not included—but other study for Wegener’s showed increase risk of solid tumors in Cytoxan treated patients
- Infliximab—increased risk of Hepatosplenic T Cell Lymphoma in children with Crohn’s on azathioprine and 6MP—and rarely in adults
- ACR hotline 6/1/2006—and updated
Anti-TNF and CHF

- Increased expression of TNF and response to treatment in animal models
- Human experience: Study using infliximab in 150 patients with Class III-IV CHF. Randomly Rx with placebo, 5, 10 mg/kg at 0,2, and 6 weeks
- No improvement despite modest increase in EF at 5mg/kg dose, BUT increased hosp. and death in 10mg/kg group.
- Role remains unclear as RA increases risk of CHF


Case Report Level

- Pancytopenia and aplasia
- Granulomatous pulmonary disease
- Vasculitis and common Injection site reactions
- SLE type glomerulonephritis

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

Novel mechanism of action
Blocks cell co-activation pathway
Approved for use in RA and in evaluation in other rheumatic diseases
Monthly infusions
Similar risks to anti-TNF but less often Tb
May be used with or without mtx
Usually after TNF “failure”—response rate 50%
Onset 4–16 weeks with improvement in fatigue and qol dramatic in some cases

Abatacept (CTLA4Ig): Mechanism of Action

Interrupts Autoimmune Response Underlying RA

CTLA4Ig Blocks Activation
Abatacept

AIM: Significant ACR Responses at 6 Months and 12 Months

†Intent-to-treat population where all dropouts were considered as ACR non-responders subsequent to their dropout

ACR responses (%)

<table>
<thead>
<tr>
<th>ACR 20</th>
<th>ACR 50</th>
<th>ACR 70</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 months</td>
<td>12 months</td>
<td>6 months</td>
</tr>
<tr>
<td>Abatacept + MTX (n=424)</td>
<td>67.9%</td>
<td>*</td>
</tr>
<tr>
<td>Placebo + MTX (n=214)</td>
<td>60.4%</td>
<td>*</td>
</tr>
</tbody>
</table>

*p<0.001

ATTAIN: Significant ACR 20, 50 and 70 Responses at 6 Months

†Intent-to-treat population, where all dropouts were considered as ACR non-responders subsequent to their discontinuation

ACR responses (%)

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<thead>
<tr>
<th>ACR 20</th>
<th>ACR 50</th>
<th>ACR 70</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 months</td>
<td>12 months</td>
<td>6 months</td>
</tr>
<tr>
<td>Abatacept + DMARDs (n=256)</td>
<td>50.4%</td>
<td>*</td>
</tr>
<tr>
<td>Placebo + DMARDs (n=133)</td>
<td>45.3%</td>
<td>*</td>
</tr>
</tbody>
</table>

*p<0.001 

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

Rituximab: Mechanism of Action

- Rituximab selectively depletes B cells bearing the CD20 surface marker via:
  - Antibody-dependent cellular cytotoxicity (ADCC)
  - Complement-dependent cytotoxicity (CDC)
  - Apoptosis

Phase III: REFLEX Trial

A&R Sept. 2006

- Randomized Evaluation of Long-Term Efficacy of Rituximab in RA
- Study Description:
  - Phase III, randomized, placebo-controlled trial
- Objectives of the Study:
  - Determine efficacy and safety of rituximab when used in combination with methotrexate
- Key Patient Eligibility Criteria:
  - Age 18–80 years
  - Diagnosed with RA for at least 6 months
  - Inadequate response to etanercept, infliximab, or adalimumab
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)

Adverse events

- Infusion reactions and length
- Infections including PML, HepB, others
- Rashes including psoriasis
- Low cell counts (wbc)
- Low IgG for long durations—significance
- Increase infections

Tocilizumab

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

- Monoclonal antibody that blocks IL6
- 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.

IL-6 Has Numerous Articular Effects in RA

- Arthritis production
- Synoviocytes
- Macrophage
- VEGF
- Endothelial cells
- Pannus formation
- Osteoclast activation
- Bone resorption


Anti-TNF, ACR70 Response Rates at Week 24
Inadequate Responders: ACR20, ACR50 ITT Population

<table>
<thead>
<tr>
<th>Treatment</th>
<th>ACR20</th>
<th>ACR50</th>
<th>ACR70</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo + MTX</td>
<td>10%</td>
<td>5%</td>
<td>1%</td>
</tr>
<tr>
<td>4 mg/kg + MTX</td>
<td>30%</td>
<td>17%</td>
<td>12%</td>
</tr>
<tr>
<td>8 mg/kg + MTX</td>
<td>50%</td>
<td>25%</td>
<td>10%</td>
</tr>
</tbody>
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** p<0.01 *** p<0.001, TCZ vs. Placebo + MTX
Newer Drugs in Development

- Newer B cell and anti-TNF agents
- p38MAP kinase inhibitors
- Janus Kinase 3 inhibitors—tocactinib
- FDA advisory board approval
- Spleen tyrosine kinase inhibitors
- Janus Kinase 3 inhibitors
- p38MAP kinase inhibitors
- Newer B cell and anti-TNF agents

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.
- A plea. Refer to confirm diagnosis and initiate treatment

Question 1

1. A 58-year-old male patient presents with polyarticular pain that has lasted for 6 weeks. He has had fevers and weight loss, and has a history of traveling to the Cape and Vineyard. He has morning stiffness, shoulder, hip and MCP pain on exam. After the usual complete history and physical performed that reveals a small knee effusion as well as above. The work need not include (not may—we are cutting the CMS budget):
   - A. CXR and hand and feet films
   - B. Lyme titer and ANA
   - C. Rheumatoid factor and anti CCP
   - D. A diagnostic tap of the knee
   - E. ESR and CRP

Answer

- A is correct
- The tap of the knee will establish whether this is an inflammatory disease or not and is the single most important test outlined. Whether the patient is seropositive or not, and/or has elevated inflammatory markers is key to guiding future therapeutics. While it is not wrong to obtain a CXR (and in fact may be done when deciding drug therapy) it is not essential at this time. Hand and feet films are unlikely to reveal anything significant after only 6 weeks of symptoms. A Lyme titer and is reasonable to obtain due to his travel in an endemic area; the ANA is really gratuitous and would not offer any diagnostic help, but I thought you should think about its role in the differential diagnosis of this patient.

Question 2

2. A 48-year-old man presents with rheumatoid arthritis. He is deciding what DMARDs to take. He has erosive disease, and has a history of travel to Russia and Peru, and has a vague sulfa allergy. His labs are unremarkable, except for a creatinine of 1.7 and an AST of 38. A. What further tests or interventions need not be done?
   - Tests:
     - a. CXR
     - b. PPD
     - c. Pneumovax
     - d. HCV and HBSAg and HBEAg
     - e. ACE level and SPEP

Answer

- E is correct
- A, B, and C must be done prior to any immunosuppressive treatment in this patient. A CXR is not mandatory in many instances, but in this man, with possible exposure to Tb, and with the additional consideration of adding methotrexate or an anti-TNF, it is imperative. Due to his travel history a PPD is imperative and hepatitis serologies are needed due to the abnormal liver blood tests, as one may consider methotrexate or rituximab (both associated with Hepatitis B reactivation syndromes). An ACE level is almost never helpful for any reason and an SPEP, while always interesting, is not needed at this juncture.
Question 3

- A 44 y/o man who is doing well on methotrexate 25mg/week for 18 months develops a cough, fever and malaise. CXR reveals a diffuse infiltrate and small pleural effusions. The next interventions need not include:
  - A. Cessation of methotrexate
  - B. Chest CT scan
  - C. Emergency Bronchoscopy
  - D. Broad Spectrum antibiotics and steroids
  - E. Sputum for C and S and methenamine silver and 1,3 beta glucan

Answer

- C. Emergency bronchoscopy
  While this may be needed eventually, other interventions should be initiated. The differential diagnosis for this man includes a CAP, Legionella, methotrexate toxicity and opportunistic infections including PCP. A chest CT will often show ground glass and a more diffuse pattern in immunosuppressed patients and should be done, as well as A,B,D, and E, among other tests including legionella antigens, LDH, ABGs, etc. If a bronchoscopy were done, one would prefer a biopsy to help diagnose methotrexate lung toxicity which often is manifested as a granulomatous inflammatory process.

References
