Disclosures

No Current Disclosures

Previous Clinical Research

- Daichi-Sankyo
- GSK
- Bristol Myers Squibb
- Wyeth
- Rigel
- Genentech/Roche
- Jazz Pharmaceuticals
- Novartis
- Centocor
Objectives

Discuss updated ACR / EULAR Recommendations for the diagnosis and treatment of Rheumatoid Arthritis

Review updated ACR Recommendations for the diagnosis and treatment of Psoriatic Arthritis and Spondyloarthritis

Discuss biologic indications and relevant updates for other autoimmune diseases
- Giant Cell Arteritis
- Granulomatosis Polyarteriitis / Microscopic Polyangiitis
- Systemic Lupus Erythematosus
RHEUMATOID ARTHRITIS

- Systemic Erosive Inflammatory Autoimmune Arthropathy
- Associated with loss of functioning in prime of life for 1-5% population
- Soft synovial swelling can be subtle and initially pallindromic
Importance of Early Diagnosis

Progressive and potentially destructive disease with multiple treatment options that can now preserve functionality, employability, independence and quality of life if detected early.

Historically 30-60% of RA patients had reduced work capacity and eventually stopped working after their diagnosis with a life expectancy of 20 years from time of diagnosis.

Early detection, referral, and treatment have improved outcomes, reduced disease severity, co-morbidity, disability, mortality and made remission possible.
Normal Joint
- Muscle
- Bone
- Synovial membrane
- Bursa
- Synovial fluid
- Joint capsule
- Cartilage
- Tendon

Osteoarthritis
- Bone erosion
- Bone ends rub together

Rheumatoid Arthritis
- Thinned cartilage
- Swollen inflamed Synovial membrane

Normal and Arthritic Joints
Stages of Rheumatoid Arthritis

1. **Synovitis**
   - Synovial membrane inflamed and thickened
   - Bones and cartilage gradually eroded

2. **Pannus**
   - Extensive cartilage loss; exposed and pitted bones

3. **Fibrous ankylosis**
   - Joint invaded by fibrous connective tissue

4. **Bony ankylosis**
   - Bones fused
## ACR/EULAR Diagnostic Criteria for Rheumatoid Arthritis

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Joint involvement</strong>*</td>
<td></td>
</tr>
<tr>
<td>1 large joint</td>
<td>0</td>
</tr>
<tr>
<td>2–0 large joints</td>
<td>1</td>
</tr>
<tr>
<td>1–3 small joints (≥ large-joint involvement)</td>
<td>2</td>
</tr>
<tr>
<td>4–10 small joints (≥ large-joint involvement)</td>
<td>3</td>
</tr>
<tr>
<td>&gt;10 joints (≥1 small joint)</td>
<td>5</td>
</tr>
<tr>
<td><strong>Serology</strong></td>
<td></td>
</tr>
<tr>
<td>Negative RF and negative ACPA</td>
<td>0</td>
</tr>
<tr>
<td>Low-positive RF or low-positive ACPA</td>
<td>2</td>
</tr>
<tr>
<td>High-positive RF or high-positive ACPA</td>
<td>3</td>
</tr>
<tr>
<td><strong>Acute-phase reactants</strong></td>
<td></td>
</tr>
<tr>
<td>Normal CRP and normal ESR</td>
<td>0</td>
</tr>
<tr>
<td>Abnormal ESR or CRP</td>
<td>1</td>
</tr>
<tr>
<td><strong>Duration of symptoms</strong></td>
<td></td>
</tr>
<tr>
<td>&lt;6 weeks</td>
<td>0</td>
</tr>
<tr>
<td>≥6 weeks</td>
<td>1</td>
</tr>
</tbody>
</table>

Total score ≥6/10 needed to classify definite rheumatoid arthritis

---

*Any swollen or tender joint on examination; excluded: distal interphalangeal joints, 1st carpometacarpal joints, and 1st metatarsophalangeal joints; large joints = shoulders, elbows, hips, knees, and ankles; small joints = metacarpophalangeal joints, proximal interphalangeal joints, 2nd–5th metatarsophalangeal joints, thumb interphalangeal joints and wrists; the >10 category can include large and small joints, and other joints not listed elsewhere (e.g., temporomandibular, acromioclavicular, or sternoclavicular); **Negative: IU values ≤ ULN for lab and assay; low-positive: IU > ULN but ≤3x ULN; high-positive: IU >3x ULN; when only RF-positive or RF-negative is known, positive scored as low-positive; †Normal/abnormal determined by local lab standards; ‡Patient self-report of duration of signs/symptoms of synovitis in joints clinically involved at time of assessment, regardless of treatment status ACPA = anti-citrullinated protein/peptide antibodies; ACR = American College of Rheumatology; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; EULAR = European League Against Rheumatism; ULN = upper limit of normal; RF=rheumatoid factor Aletaha D et al. Arthritis Rheum 2010; 62(9):2569-81.*
Labs

**Rheumatoid Factor (RF)**
- Positive test in ~75% of patients with RA
- Occasionally occurs in other inflammatory diseases
- Not an accurate measure of disease progression

**Anti-CCP antibodies**
- Anti-cyclic citrullinated peptide antibodies
- Highly specific for RA (90%)
- Correlates well with disease progression

**Erythrocyte sedimentation rate (ESR)**
- Measures how rapidly red blood cells settle
- Elevated in RA
- Useful to monitor disease course

**C-reactive protein (CRP)**
- Serum protein that increases rapidly after tissue injury, indicating acute inflammation (typically >0.7 mg/dL)
- May be used to monitor disease course
Imaging Recommendations

Although most pharmacologic clinic trials continue to use x-ray changes ie. Erosions - to show inhibition of radiographic progression, the presence of erosions can mean the early window for intervention has been lost.

US and MRI have allowed for the detection of synovitis, pannus, osteitis, effusions, tenosynovitis and early erosion measurements to the millimeter.

This is useful in making a diagnosis of RA or of an undifferentiated erosive inflammatory arthritis and helping to predict rate of progression.
MRI and US are both more sensitive in detecting these early inflammatory changes and erosions.

Accurate measurement of the changes with comparisons over time can help guide treatment decisions and help predict outcomes.

EULAR considers MRI or US bone edema/osteitis/erosions as a strong independent predictor of progression to joint damage and a prognostic indicator.

US and MRI can confirm clinical remission or assess persistent inflammation.
RA Is a Progressive Disease

- Early
- Intermediate
- Late

Severity

Duration of Disease (Years)

Inflammation
Disability
Radiographs

2015 ACR RA Guidelines

What Is Covered

- Traditional DMARDs (MTX, LEF, SSZ, HCQ)
- Biologic DMARDs (TNFi, abatacept, tocilizumab, rituximab)
- Tofacitinib
- Glucocorticoid therapy
- Treat-to-target approach
- Tapering/discontinuing medications
- High-risk populations: hepatitis B and C, congestive heart failure, malignancy, recurrent serious infections
- Use of vaccines
- Screening for tuberculosis
- Laboratory monitoring of therapy

2015 ACR RA Guidelines

• Similarities with previous guidelines:
  – Frequent disease activity assessments, treatment escalation or switching, targeting the most optimal outcome for the patients

• New aspects of the 2015 guidelines:
  – Uses GRADE Methodology vs Rand UCLA Appropriateness Method
  – Includes new types of therapies
  – Discusses care for certain high-risk patient populations
  – Provides guidance on tapering and discontinuation to meet patient-desired goals
  – Makes recommendations based on patients' disease activity level only (vs both disease activity and prognosis)

Epigenetic Changes

Predisposing Factors

Immune Modulators
- HLA-DR4 shared epitope
- Additional genetic risk factors
- Ratio of Omega 6:3 fatty acids
- Vitamin D3, trace minerals
- Disruption of microbiome

Environmental Factors
- Smoking
- Air pollution
- Pesticides/Herbicides
- Volatile organic compounds
- Clearance (GST1<sup>null</sup>)

RA Trigger

Triggering Events
- Physical Trauma
- Smoke
- Infections
- Food Sensitivities
- Environmental toxins

Emotional Trauma

RA
- T Cells
- TNFα, IL-1, IL-6, IL-17
- CD20+ B Cells
- Mast cells
- Dendritic cells
Pathogenesis of Rheumatoid Arthritis

Antigen (?) microbe

MHC class II (genetic susceptibility)

CD4+ T cells

Cytokines, e.g. TNF

B-cell activation

Formation of rheumatoid factor, her autoantibodies

Immune complex formation and deposition

Joint injury

Macrophage activation

Cytokines, e.g. TNF

IL-1

Fibroblasts

Chondrocytes

Synovial cells

Release of collagenase, stromelysin, elastase, and other enzymes

Pannus formation; destruction of bone, cartilage; fibrosis; ankylosis

PGE2

Endothelial activation

Expression of adhesion molecules

Accumulation of inflammatory cells

Proliferation
- The interactions between antigen-presenting cells (APCs) and T lymphocytes (T cells) affect early stages in the pathogenic cascade of events in RA
- B cells are important to the inflammatory process with multiple functions in the immune response
  - The depletion of B cells has been shown to be effective in reducing signs and symptoms of RA
- Tumor necrosis factor alpha (TNF-α) is a pro-inflammatory cytokine produced by macrophages and lymphocytes
  - It is found in large quantities in the rheumatoid joint
  - TNF-α is one of the critical cytokines that mediate joint damage and destruction
# Early and Mild RA Therapies

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Actions and Effects</th>
</tr>
</thead>
</table>
| **NSAID and COX-2 inhibitors** | - Reduces joint pain and inflammation  
- No effect on progression of disease  
- GI and CV side effects |
| **Oral steroids**      | - Relieve pain and inflammation  
- May slow disease progression, work quickly  
- May work as a bridge therapy until others reach efficacy  
- Long-term use associated with many side effects including osteoporosis, skin fragility, diabetes, Cushing’s disease, atherosclerosis |
| **DMARDs (Disease Modifying Antirheumatic Drugs)** | - May slow progression of disease  
- May take 4–24 weeks to obtain clinical benefit  
- Side effects variable and based on DMARD prescribed  
- Methotrexate, leflunamide, hydroxychloroquine, azathioprine, sulfasalazine, cellcept, minocycline |
Initiating Treatment for Early and Established RA

- Low, moderate, or high disease activity
  - Start with traditional DMARD monotherapy (ie, methotrexate)
  - Regular assessment of disease activity
- If RA is uncontrolled
  - Combination traditional DMARDs, or
  - TNFi +/- MTX, or
  - Non-TNFi biologic +/- MTX, or
  - Tofacitinib +/- MTX (in established RA only)
- If patient experiences an RA flare, use lowest possible dose of short-term glucocorticoids

Biologics for Moderate/Severe RA

TNF inhibitors
- Infliximab
- Etanercept
- Certolizumab pegol
- Adalimumab
- Golimumab

Other biologic agents
- IL-1
  - Anakinra
  - IL-1 signaling
- IL-6
  - Tocilizumab
  - IL-6 signaling

Antigen
- MHC
- T-cell receptor
- Co-stimulatory signal

Rituximab
- CD20
- B-cell depletion
TNF Inhibitors

**Etanercept (Enbrel)**
- Humanized recombinant rec FC fusion protein
- 50 mg SC injectable weekly
- Approved for RA, JIA, Psoriasis, Psoriatic arthritis, ankylosing spondylitis

**Infliximab (Remicade)**
- Chimeric monoclonal antibody
- Administered 3-10mg/kg intravenous via a 2 hour infusion every 4 to 8 weeks
- Approved for RA, Psoriasis, Psoriatic arthritis, ankylosing spondylitis, Crohn’s disease, Ulcerative Colitis

**Adalimumab (Humira)**
- Humanized monoclonal antibody
- 40mg SC injectable every 2 weeks
- Approved for RA, JIA, Psoriasis, Psoriatic arthritis, ankylosing spondylitis, Crohn’s disease, Ulcerative Colitis, Hidradenitis Suppurativa, Uveitis

**Certolizumab Pegol (Cimzia)**
- Humanized Fab’ fragment
- Two 200mg SC injectables monthly – at home or in-office Lyo form
- Approved for RA, Psoriatic arthritis, Ankylosing Spondylitis and Crohn’s disease

**Golimumab (Simponi)**
- Humanized monoclonal antibody
- 50mg SC injectable monthly or iv as Aria- every 8 weeks
- Approved for RA, Psoriatic arthritis, Ankylosing Spondylitis, Ulcerative Colitis
TNF Inhibitors

- **Chimeric monoclonal antibody**: infliximab IgG1
- **Humanized monoclonal antibody**: CDP571 IgG4
- **Human recombinant antibody**: adalimumab IgG1, golimumab IgG1, certolizumab pegol
- **Humanized Fab’ fragment**: etanercept IgG1
- **Human recombinant receptor/Fc fusion protein**:

*CDR = Complementarity-determining region; PEG = polyethylene glycol*

Naming mAb: (1) first 2-4 letters = WHO/sponsor picks; (2) middle part: disease/target (eg, immune = lim-; cardiac = cir-); (3) type of antibody (-omab = murine, -ximab = chimeric, -zumab = human, -umab = human).

Permission to use from Arthur Kavanaugh, MD.
B and T Cell RA Tx

Rituximab (Rituxan)

- CD20 B cell directed cytolytic antibody therapy approved for RA
- Administered in two 500mg 4-8 hour infusions, 2 weeks apart every 6 months
- Approved for RA, GPA/MPO vasculitis and Non-Hodgkin’s Lymphoma – 6/17 FDA approved SQ

Abatacept (Orencia)

- T cell costimulation inhibitor
- Monthly 30 minute weight based infusion or weekly SQ 125mg
- Approved for RA, JIA, PsA
IL-6 and Jak RA Tx

**Tocilizumab (Actemra)**
- Interleukin-6 IL-6 receptor inhibitor
- Administered monthly via a 4-8mg/kg 30 minute infusion or SQ every 2 weeks
- Approved for RA, Giant Cell Arteritis, PJIA, SJIA

**Sarilumab (Kevzara) FDA approved 5/17**
- Monoclonal ab that binds Interleukin-6R and inhibits mediated signaling
- Administered 150-200mg SQ q 2 weeks
- Approved for RA

**XELJANZ® (tofacitinib)**
- Oral Janus kinase inhibitor
- Oral 5mg BID or 11mg XR Daily
- Approved for RA (pending PsA, psoriasis)
Figure 3 Site of action of antirheumatic drugs on osteoclast differentiation and bone erosion

Denosumab Mechanism of Action

Growth Factors
Hormones
Cytokines

Bone

CFU-M = colony forming unit macrophage

RANKL
RANK
OPG
Dmab

Pre-Fusion
Osteoclast
Multinucleated
Osteoclast
Osteoclast

RANKL

Osteoblast
Lineage
Bone
Denosumab (Prolia®) (Anti-resorptive agent)

Amgen – 60mg/ml SQ every 6 months administered in-office

Fully human monoclonal antibody biologic that binds with high affinity to, and inhibits the activity of, human RANK ligand, a key mediator of osteoclast activity

Indicated for the treatment of postmenopausal women with osteoporosis and men at high risk for fracture
Biologic Selection

Currently, it is not possible to identify the key cytokine responsible for perpetuating RA in individual patients.

Some patients have a preference for one agent over another, based on route of administration, dosing frequency, co-morbidities or past medical history.

Insurance companies often require one particular agent be used before trying others – Step Therapy.

Most have comparable evidence of safety, efficacy and side effects.
Vectra DA
multi-biomarker blood test
FOR RA
Vectra DA — is a serologic lab test that measures the concentrations of 12 serum proteins and applies an algorithm to calculate a single Vectra DA score ranging from 1 to 100 that categorizes RA into low, moderate, or high disease activity.

Vectra DA can provide a baseline assessment of RA disease activity, track it over time and provide guidance for treatment options.
 Vectra DA

**TEST RESULTS**

*Vectra DA Score = 19*  
(95% Range: 16.5 - 21.5)

SAMPLE TEST REPORT

Only test results from the previous 10 months are shown.

**VECTRA DA SCORE**

- High
- Moderate
- Low

**SPECIMEN COLLECTION DATE**

- OCT-01-2010: 55
- DEC-02-2010: 35
- MAR-02-2011: 20
- APR-05-2011: 19
Considerations Prior to Treatment

- ppd testing and/or a chest
- Assess for other co-morbidities
- Vaccinate patients with any necessary live virus vaccines ex. Zostavax. Killed virus vaccines are recommended afterwards with precautions and proper scheduling
- Hepatitis panel and parvovirus testing
- Ask about risk factors for histoplasmosis, coccidiomycosis - fungal infections
Considerations During Treatment

- Get annual ppd vs. CXR vs. Quantiferon
- Hold biologics 2 weeks prior and after elective surgeries or until the surgeon clears the patient
- Postpone next dose during infection. Resume only once resolved. Have a low threshold for treating infections with antibiotics, antifungals and antivirals.
Considerations During Treatment

- Routine monitoring of CBC, CMP, ESR and CRP with additional serology depending upon the specific biologic medication utilized ex. lipids, neutrophils, autoantibodies, quantitative immunoglobulins

- Check cervical flexion and extension views for patients with long standing disease prior to surgery with general anesthesia involved
# ACR Criteria in Determining Remission of RA

≥5 of conditions below for at least 2 consecutive months

- Duration of morning stiffness not exceeding 15 minutes
- No fatigue
- No joint pain
- No joint tenderness or pain with motion
- No soft-tissue swelling in joints or tendon sheaths
- ESR of less than 30 mm/h in a female or less than 20 mm/h in a male

Foods For Arthritis & Inflammatory Pain

**Cherries**
Contains anthocyanocides which help lower uric acids levels reducing pain

**Ginger**
Ginger contains gingerols which are potent anti-inflammatory compounds. Eat more fresh ginger or drink ginger root tea.

**Pineapple**
Contains Bromelain which is an effective anti-inflammatory

**Turmeric**
Contains curcumin which is an anti-oxidant & anti-inflammatory.

**Raw Apple Cider Vinegar**
Contains helpful anti-inflammatory properties. 1 Tbsp in 6-8 ounces of water, or use as part of a salad dressing.

**Omega 3’s**
Contains anthocyanocides which help lower uric acids levels reducing pain. Eat more chia, fish, hemp, and flax seeds.

**Avoid**

**Sugar Foods**
Leads to increased AGES (toxins causing inflammation), which results in more aches and pains

**Fried Foods**
Overcooked food or foods cooked at high temperatures incite the inflammatory response because they create AGES

**Omega 6 oils**
High intake of omega 6 increases inflammation in the body. Replace foods containing omega-6s with healthier omega 3 foods.

**Salt**
For some people excess sodium consumption can inflame the joints. Less salt may help arthritis symptoms.
Psoriatic arthritis

Classification Criteria for Psoriatic Arthritis (CASPAR) - inflammatory articular disease with at least 3 points:

- Current psoriasis (assigned a score of 2)
- History of psoriasis (in the absence of current- 1)
- Family history of psoriasis (in the absence of current and history- 1)
- Dactylitis (1)
- Juxta-articular new-bone formation (1)
- RF negativity (1)
- Nail dystrophy (1)
Table. The CASPAR classification criteria for PsA

To be classified as having PsA, a patient must have inflammatory articular disease (joint, spine, enthesal) with ≥ 3 of the following 5 points:

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Evidence of psoriasis (one of a, b, c):&lt;br&gt;(a) Current psoriasis&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Psoriatic skin or scalp disease currently present, as judged by a rheumatologist or a dermatologist</td>
</tr>
<tr>
<td>(b) Personal history of psoriasis</td>
<td>A history of psoriasis obtained from patient or family physician, dermatologist, rheumatologist, or other qualified healthcare professional</td>
</tr>
<tr>
<td>(c) Family history of psoriasis</td>
<td>A history of psoriasis in a first- or second-degree relative by patient report</td>
</tr>
<tr>
<td>2. Psoriatic nail dystrophy</td>
<td>Typical psoriatic nail dystrophy, including onycholysis, pitting, and hyperkeratosis observed on current physical examination</td>
</tr>
<tr>
<td>3. Negative test result for RF</td>
<td>By any method except latex but preferably by ELISA or nephelometry, according to the local laboratory reference range</td>
</tr>
<tr>
<td>4. Dactylitis (one of a, b):&lt;br&gt;(a) Current</td>
<td>Swelling of an entire digit</td>
</tr>
<tr>
<td>(b) History</td>
<td>A history of dactylitis recorded by a rheumatologist</td>
</tr>
<tr>
<td>5. Radiological evidence of juxta-articular new bone formation</td>
<td>Ill-defined ossification near joint margins (excluding osteophyte formation) on plain x-ray films of hand or foot</td>
</tr>
</tbody>
</table>

CASPAR, CIASsification criteria for Psoriatic ARthritis; PsA, psoriatic arthritis; RF, rheumatoid factor; ELISA, enzyme-linked immunosorbent assay.

<sup>a</sup> Current psoriasis scores 2; all other items score 1.
Guttate, pustular, inverse, eczematous
PsA and Spondyloarthropathies

- Enthesopathy, enthesitis, inflammation at tendon or ligament insertions into bone - attachment of the Achilles tendon and the plantar fascia to the calcaneus - insertional spurs, osteophytes

- Dactylitis with sausage digits is seen in as many as 35% of patients
Nail findings may be solitary

- Beau lines
- Leukonychia
- Onycholysis
- Oil spots
- Subungual hyperkeratosis
- Splinter hemorrhages
- Spotted lunulae
- Transverse ridging
- Cracking of the free edge of the nail
- Uniform nail pitting
LAB Findings

- Immunoglobulin genes – HLA-B27 and others
- High serum immunoglobulin A (IgA) and IgG – IgM normal or diminished.
- Hyperuricemia – high cell turn-over state
- Low levels of circulating immune complexes have been detected in 56% of patients
- Complement levels – normal or increased
- RF negative
Psoriatic arthritis Patterns

1. Symmetrical polyarthritis
2. Asymmetrical oligoarticular arthritis
3. Distal interphalangeal arthropathy
4. Arthritis mutilans
5. Spondylitis with or without sacroiliitis
Spondyloarthropathies

- **Seronegative refers to a negative RF**
- **Spondylitis - radiographically or not - is a linking feature**
<table>
<thead>
<tr>
<th>Feature</th>
<th>PsA</th>
<th>RA</th>
<th>OA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inflammatory arthritis</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Peripheral involvement</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Axial involvement (sacroiliac joint, spine)</td>
<td>Yes</td>
<td>No (only C1-2 and occasional C spine)</td>
<td>Possible</td>
</tr>
<tr>
<td>Symmetrical involvement</td>
<td>Rare</td>
<td>Yes</td>
<td>Variable</td>
</tr>
<tr>
<td>DIP joint involvement</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Enthesitis</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Dactylitis</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Erosions and new bone formation</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Skin involvement</td>
<td>Most of the time</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

PsA, psoriatic arthritis; RA, rheumatoid arthritis; OA, osteoarthritis; DIP, distal interphalangeal.

* One variant, inflammatory OA, may manifest focal erosion and new bone formation.
PsA: Revised Treatment Strategy

Psoriatic arthritis

- Skin
- Axial
- Peripheral
- Enthesopathy
- Dactylitis

Assess phenotypes

Assess imaging, activity and erosion markers

Comorbidities

- Plain X-ray
- DPUS, MRI
- Acute phase reactants
- Cellular and serum biomarkers

Erosions: imaging and/or markers

No erosions

Treatment guided by clinical features, imaging and biomarkers

Monitor treatment response, change in biomarkers and imaging studies

Monitor and adjust Rx
Which domains are involved?

Peripheral arthritis
- DMARDs (MTX, SSZ, LFN, TNFi, PDE4)
  - Biologics (TNFi, IL12/23, IL17i)
  - Switch Biologic (TNFi, IL12/23, IL17i)
- NSAIDs and IA corticosteroids as indicated

Axial Disease
- DMARDs (MTX, LFN, TNFi)
  - NSAIDs only
  - Switch Biologic (TNFi, IL12/23, IL17i)
- Physiotherapy and NSAIDs

Enthesitis
- DMARDs (MTX, SSZ, LFN, TNFi, PDE4)
  - NSAIDs
- Biologics (TNFi, IL12/23, IL17i)
  - Switch Biologic (TNFi, IL12/23, IL17i)
- Physiotherapy

Dactylitis
- DMARDs (MTX, LFN, TNFi, PDE4)
  - NSAIDs
  - Biologics (TNFi, IL12/23, IL17i)
  - Switch Biologic (TNFi, IL12/23, IL17i)

Skin
- Topicals (keratolytics, steroids, vit D analogues, emollients, calcineurin inhibitors)
  - Phototherapy or DMARDs (MTX, CSA, Actetretin, Fumaric acid esters)
  - Topical or Procedural (CSA, LFN, MTX, Actetretin)

Nails
- Biologics (TNFi, IL12/23, IL17i)
  - Topical or Procedural (CSA, MTX, Actetretin)
  - Switch Biologic (TNFi, IL12/23, IL17i)

Assess activity, impact and prognostic factors

No direct evidence for therapies in axial SpA, recommendations based on axial SpA literature.

Consider previous therapy, patient choice, other disease involvement and comorbidities. Choice of therapy should address as many domains as possible.

Treat, periodically re-evaluate and modify therapy as required.

KEY
- Standard Therapeutic Route
- Expedited Therapeutic Route
TREATMENTS

Corticosteroids, NSAIDS, DMARDs – similar to RA but not FDA approved

Tumor necrosis factor (TNF) blockers - Etanercept, Infliximab, Abatacept, Golimumab and Certolizumab

Interleukin-12/interleukin-23 inhibitor - Ustekinumab (Stelara) - SQ quarterly (45mg-90mg) also for Crohn’s Disease
TREATMENTS

- **T cell costimulation inhibitor, Abatacept (Orencia)** - Monthly 30 minute weight based infusion or weekly SQ 125mg - Approved for RA, JIA, PsA approved 7/17

- Phosphodiesterase 4- PDE4 inhibitor- Apremilast (Otezla) - oral 30mg BID

- Interleukin-17A inhibitor- Cosentyx (secukinumab) - SQ monthly (150mg- 300mg) approved 1/16 also for AS
Otezla® (apremilast)
unique oral small-molecule inhibitor of phosphodiesterase 4 specific for cyclic adenosine monophosphate (cAMP) - increases intracellular levels
Biologics Indicated for other Autoimmune Diseases and a Review of those Conditions
Tocilizumab (Actemra) for GCA

First FDA approved treatment for Giant Cell Arteritis - May 2017

Subcutaneous dosing only

Tocilizumab for induction and maintenance of remission in giant cell arteritis: a phase 2, randomised, double-blind, placebo-controlled trial

Peter Wilfinger, Sabine Adler, Stefan Kucher, Felix Ronneberger, Diana Chen, Norikazu Ito, Lukas Buhlker, Michael Sattel, Stephan Henckel

Summary

Background Giant cell arteritis is an immune-mediated disease of medium and large-sized arteries that affects mostly people older than 50 years of age. Treatment with glucocorticoids is the gold-standard and prevents severe vascular complications but is associated with substantial morbidity and mortality. Tocilizumab, a humanised monoclonal antibody against the interleukin-6 receptor, has been associated with rapid induction and maintenance of remission in patients with giant cell arteritis. We therefore aimed to study the efficacy and safety of tocilizumab in the first randomised clinical trial in patients with newly diagnosed or recurrent giant cell arteritis.

Methods

In this single centre, phase 2, randomised, double-blind, placebo-controlled trial, we recruited patients aged 50 years and older from University Hospital Bern, Switzerland, who met the 1990 American College of Rheumatology criteria for giant cell arteritis. Patients with new-onset or relapsing disease were randomly assigned (2:1) to receive either tocilizumab (8 mg/kg) or placebo intravenously. 13 infusions were given in 4 weeks intervals until week 52. Both groups received prednisolone, starting at 1 mg/kg per day and tapered down to 0 mg according to a standard reduction scheme defined in the study protocol. Allocation to treatment groups was done using a central computerised randomisation procedure with a permuted block design and a block size of three, and concealed using central randomisation governed by the clinical trials unit. Patients, investigators, and study personnel were masked to treatment assignment. The primary outcome was the proportion of patients who achieved complete remission of disease at 52 weeks and a cumulative prednisone dose of 0 mg/kg per day at week 12. All analyses were intention to treat. This trial is registered with ClinicalTrials.gov, number NCT01658317.

Results

Between March 3, 2012, and Sept 9, 2014, 20 patients were randomly assigned to receive tocilizumab and prednisolone, and ten patients to receive placebo and glucocorticoids. 36 (84%) and seven (75%) patients, respectively, had new-onset giant cell arteritis; 17 (75%) of 20 patients given tocilizumab and four (40%) of ten patients given placebo reached complete remission by week 12 (risk difference 45%, 95% CI 11–79; p=0.001). Remission-free survival was achieved in 17 (85%) patients in the tocilizumab group and two (25%) in the placebo group by week 52 (risk difference 63%, 95% CI 26–94; p=0.009). The mean survival time to stop glucocorticoids was 32 weeks in favour of tocilizumab (95% CI 7–73; p=0.001) leading to a cumulative prednisolone dose of 43 mg/kg in the tocilizumab group versus 108 mg/kg in the placebo group (p=0.001) after 52 weeks. Seven (35%) patients in the tocilizumab group and five (50%) in the placebo group had serious adverse events.

Interpretation

Our findings show, for the first time in a trial setting, the efficacy of tocilizumab in the induction and maintenance of remission in patients with giant cell arteritis.

Funding Roche and the University of Bern.

Introduction

Giant cell arteritis is characterised by a destructive, granulomatous inflammation of the walls of medium and large-sized arteries. Annual incidence varies between six and 12 cases per 100,000 people worldwide. 1 Glucocorticoids are the gold-standard for controlling symptoms and reducing the risk of vascular complications, such as blindness. However, necessary doses and long duration of treatment invariably lead to high morbidity and substantial mortality. 2 Neither conventional immunosuppressive drugs nor biological agents effectively induce remission, and the extent of their steroid-sparing effect during maintenance, for instance with methotrexate, remains a matter of debate.3 Interleukin-6 induces acute phase responses and has a central role in the pathogenesis of giant cell arteritis. 4 5 Serum and tissue samples of patients with this disorder showed increased concentrations of interleukin-6. 6 7 Tocilizumab, used to treat rheumatoid arthritis and juvenile rheumatoid arthritis, 8 9 is a humanised immunoglobulin G1 kappa monoclonal antibody that blocks signalling by binding to the alpha chain of the human interleukin-6 receptor. 10 Results of several case studies have shown rapid induction and maintenance of remission of giant cell arteritis using tocilizumab. 11 We therefore decided to do the first randomised, placebo-controlled trial to study the efficacy and safety of induction and maintenance of
Giant cell arteritis (GCA) can alternatively be called cranial arteritis or temporal arteritis, reflecting the most commonly affected vessels.

GCA is the inflammation of the lining of the arteries and is a relatively common vasculitis among older adults.

Common symptoms of GCA include blurring or loss of vision, headaches, and jaw pain. Other areas such as the head and neck can also be affected by GCA.

Histologically, the tunica media thickens and the lumen narrows due to tunica interna fibrosis. Inflammatory cells can be seen invading the tunica media, especially lymphocytes and eosinophils. Giant cells can occasionally be seen populating areas around the internal elastic membrane.
<table>
<thead>
<tr>
<th></th>
<th>ACR Classification Criteria for Giant Cell Arteritis</th>
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<tbody>
<tr>
<td>1.</td>
<td>Age more than 50 years;</td>
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<tr>
<td>2.</td>
<td>New-onset headache;</td>
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<tr>
<td>3.</td>
<td>Temporal artery abnormalities (e.g., irregularities of the arterial wall);</td>
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<td>4.</td>
<td>Erythrocyte sedimentation rate (ESR) greater than 50 mm/hour; and</td>
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<tr>
<td>5.</td>
<td>Histologic evidence of arteritis on temporal artery biopsy (e.g., mononuclear cell infiltration or granulomatosus inflammation).</td>
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</tbody>
</table>
IL-6 Signaling Inhibition

DECREASES
Acute-phase reactants, eg, CRP, ESR

LOWERS
Hepcidin production

REDUCES
B-cell activation

IMPROVES
Profiles of bone and cartilage turnover markers

INHIBITS
Differentiation of T-helper cells into Th17 cells

DECREASES
CRP and ESR

INCREASES
Hb

DECREASES
RF

REDUCES
Bone resorption and cartilage turnover

INHIBITS
Formation of inflammatory Th17 cells
Giant Cell Arteritis Treatment

1st line corticosteroid

Takayasu A.

1st line MTX*
2nd CP, AZA, MFM

GCA

2nd line MTX
3rd CP, AZA, MFM

Refactory patient

3rd/4th lines Biological Tx

i. Tocilizumab/Anti TNF
ii. Rituximab?
iii. Abatacept?

i. Tocilizumab
ii. Anti TNF
iii. Rituximab?
iv. Abatacept?
Rituximab for Granulomatosis with Polyangiitis and Microscopic Polyangiitis

Cyclophosphamide was previously the most effective treatment for severe vasculitis disease
- Some patients were refractory to the treatments
- CTX may be contraindicated in or not tolerated by some patients
- Side effects can be excessive – ovarian failure, hemorrhagic cystitis, bladder cancer

B lymphocytes play a central pathogenic role

ANCA are produced by short-lived plasma cells and play a role in the pathogenesis

Depletion of CD20+ haults ANCA production
Systemic Lupus Erythematosus

Autoimmune disease that is associated with B-cell hyperactivity, autoantibodies, and increased concentrations of B-lymphocyte stimulator (BLyS)
Systemic Lupus Erythematosus

- Multisystem disease involving clinical and immunologic lab abnormalities observed over time
- Recurrent oral ulcers
- Interarticular dermatitis with periungual erythema
- Butterfly rash sparing nasolabial folds
### 2012 SLICC Classification Criteria for Systemic Lupus Erythematosus

**Biopsy proven LUPUS NEPHRITIS and ANA or anti-DNA**

<table>
<thead>
<tr>
<th>CLINICAL</th>
<th>IMMUNOLOGIC</th>
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<tbody>
<tr>
<td>Acute cutaneous LE</td>
<td>ANA</td>
</tr>
<tr>
<td>Chronic cutaneous LE</td>
<td>Anti-dsDNA</td>
</tr>
<tr>
<td>Oral ulcer</td>
<td>Anti-Sm</td>
</tr>
<tr>
<td>Alopecia</td>
<td>aPL antibodies</td>
</tr>
<tr>
<td>Synovitis</td>
<td>Low complement</td>
</tr>
<tr>
<td>Serositis</td>
<td>Direct Coomb’s test</td>
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<tr>
<td>Renal</td>
<td></td>
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<tr>
<td>Neurologic</td>
<td></td>
</tr>
<tr>
<td>Hemolytic anemia</td>
<td></td>
</tr>
<tr>
<td>Leucopenia/ lymphopenia</td>
<td></td>
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<tr>
<td>Thrombocytopenia</td>
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</table>

**AT LEAST 4 CRITERIA**

(1 Needs to be IMMUNOLOGIC)

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Belimumab - Benlysta®

First targeted biological treatment for SLE- indicated for adult patients with active, autoantibody-positive, systemic lupus erythematosus who are receiving standard therapy

BLyS-specific inhibitor that blocks the binding of soluble BLyS, a B-cell survival factor, to its receptors on B cells

First Drug approved in 50 years – Prior Hydroxychloroquine (Plaquenil)

Infusion given over 30 minutes q4 weeks after loading doses

Not for lupus nephritis though
Thank You

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