Rheumatoid arthritis Management update

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ACP Arkansas Chapter meeting 2018
Disclosures

- Nothing to disclose
Objectives

- The importance of early diagnosis and treatment of rheumatoid arthritis
- Treat to target concept
- Recognize comorbidities when choosing DMARDs and biologics
Rheumatoid arthritis

- Progressive autoimmune inflammatory symmetric polyarthritis
- Affects about 0.5%-1% of US population
  - If left untreated can lead to joint destruction, disability, morbidity and mortality
- More in females
- Peak onset 30 and 50 years of age
SEVERE RA DEFORMITIES
Rheumatoid arthritis
Risk factors

- genetics
- Infectious agents
- Smoking
- Formal education
- hormones
RA
articular symptoms

- Inflammatory pain, usually symmetric
- Swelling
- Arm stiffness
- Redness
- Warmth
extra articular symptoms

- Ocular
- ENT
- SKIN
- Oral
- Pulmonary
- Cardiac
- Vasculitis
- Neurologic
- Hematologic
- Renal
RA

Poor prognostic factors

- Functional limitation
- Extraarticular disease
- Rheumatoid factor positivity or presence of anticyclic citrullinated peptide (CCP) antibodies
- Bony erosions documented radiographically
Rheumatoid arthritis pathogenesis

- pathogenesis is complex
  - Many types of cells involved including and not limited to
    - Macrophages
    - T cells and B cells
    - Fibroblasts
    - Chondrocytes
    - Dendritic cells
1987 ACR revised criteria for RA

<table>
<thead>
<tr>
<th>1. Morning stiffness</th>
<th>At least 1 hour</th>
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<tbody>
<tr>
<td>2. Arthritis of three or more joints</td>
<td>At least in 3 joint areas out of 14 possible areas (PIP, MCP, wrist, elbow, knee, ankle, MTP)</td>
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<td>3. Arthritis of hand joints</td>
<td>At least one area swollen in a wrist, MCP or PIP joint</td>
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<td>4. Symmetric arthritis</td>
<td>Simultaneous involvement of the same areas of both sides of the body</td>
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<tr>
<td>5. Rheumatoid nodules</td>
<td>Observed by a physician</td>
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<td>6. Serum RF</td>
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<td>7. Radiographic changes</td>
<td>Erosions, juxta articular osteopenia</td>
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2010 ACR/ EULAR classification criteria

- Large joint count: 2 or more jnts (0-1)
- Small joint count: 1- >10 joints (2-5)
- Serum RF or CCP: low or high (2-3)
- Symptom duration: 6 weeks (0-1)
- Elevated CRP or ESR: (0-1)

6/10 or more is required for Dx of definite RA
The advantages of 2010 ACR calcification criteria

- It only needs at least 1 joint synovitis, which can not be explained by other diseases
- The number of joints involved matter
- The duration of the symptoms for more than 6 weeks has higher score
- Morning stiffness, nodules and x-ray changes are not included
- Leads to early dx and tx of RA
Case presentation

- 26 year old female who was referred for positive RF and arthralgia x 7 weeks.
- She denies fever, GU symptoms. Respiratory symptoms, rash, Raynaud’s, sicca symptoms. Denies recent travel.
- Joints involved hands, knee and feet with synovitis of 6 small and 1 large joints.
- Labs serum RF 50 (nl <14), sed rate 36, CRP 5.1 (nl<0.5). CCP ab <20
- Does she meet the 2010 criteria for RA?
- Any other tests need to be ordered?
Case presentation

She met the definite RA criteria
- 0 point for 1 large joint
- 3 points for 6 small joints
- 3 points for hi RF
- 1 point for >6 weeks duration
- 1 point for elevated sed rate and CRP
Rheumatoid arthritis
Non pharmacologic treatment

- Patient education
- Stress management, diagnose and treat anxiety and depression
- Diagnose and treat sleep disorders
- Exercise
- Heart healthy diet
- Smoking cessation
- Screening for and treatment of osteoporosis
- Immunizations
Case presentation

- 60-y/o female who presented with 6 month hx of pain in both hands and feet which worsened gradually. She denies any injuries. Her symptoms are associated with morning stiffness x 1 hour. She has redness and swelling in multiple joints of both hands and feet. She denies any history of infection, STDs, GI symptoms, urinary and respiratory symptoms.

- Past medical history: Type 2 diabetes with hemoglobin A1C 9.2, complicated by retinopathy. She also has macular degeneration.

- Allergies: Aspirin (rash and respiratory sx)

- Family History: Noncontributory

- Medications: Insulin, metformin and Lisinopril

- Review of System: Negative, except what's mentioned above

- Physical Examination: Vital signs are normal, general exam is normal

- Musculoskeletal Exam: Significant for Synovitis of bilateral MCPs, PIPs, and MTP joints. TSJ 14. Total tender joints 21

- Lab tests showed normal CBC, CMP, Hepatitis panel, SED rate was elevated at 60. CRP was elevated at 10 (normal is less than 0.5).

- Rheumatoid factor was 225. CCP antibody 120. ANA was negative. X-Rays of both hands, feet and chest were normal.

What is her dx?
Case presentation

- The diagnosis of Rheumatoid Arthritis was made. Scored 10/10 on ACR classification criteria
- What is the best next step in management?
  1. Start sulfasalazine
  2. Start hydroxychloroquine
  3. Start methotrexate or leflunomide
  4. Start low dose steroids
The correct answer is answer # 3. The patient has seropositive rheumatoid arthritis with positive CCP antibody. Current recommendations stress on the importance of the early detection and treatment of rheumatoid arthritis.

- Sulfasalazine is contraindicated due to the documented history of allergy to aspirin.
- Hydroxychloroquine is not recommended given the patient’s h/o retinopathy and macular degeneration
- Steroids are not recommended due to the patient’s history of uncontrolled diabetes.

References:
Rheumatoid arthritis treatment goals

- Remission
- Reduce inflammation
- Decrease/prevent deformities
- Maintain function
- Decrease pain
- Improve quality of life

**CONCLUSION:**
Greater duration of exposure to DMARD soon after RA diagnosis was associated with delays to joint replacement surgery in both provinces. Early intensive treatment of RA may ultimately reduce demand for joint replacement surgery.
Rheumatoid arthritis pharmacologic treatment

- In EARLY 1980s the treatment approach for RA was:
  1. Anti-inflammatory medications (ASA, NSAIDs)
  2. steroids
  3. SAARD
     Antimalarials
     Penicillamine
     Azathioprine
     Cyclophosphamide
     Gold salts
  4. Hospitalization
  5. Surgery
Available DMARDs for RA

- Methotrexate
- Sulfasalazine
- Leflunomide
- Hydroxychloroquine
- Azathioprine
- Cyclosporine
Methotrexate

- Approved for RA in 1988
- Dosed once weekly
  - Oral dose between 7.5 to 20 mg weekly
- Split oral dose if >15 mg
- SC/IM dose 7.5 to 25 mg weekly
- MTX polyglutamate level is rarely used to check compliance
- B12 2 days prior to MTX can help fatigue
- Mucinex DM the day Of MTX, then the day after helps CNS AE
- Folic acid helps most AE
- Vitamin A 8000 units daily can helps oral ulcers
Non biologic DMARDs

- SSZ: main AE is GI, monitor for anemia and renal function
- Leflunomide: main AE is GI, HA, hair loss, ?pulmonary monitor for cytopenia, and liver function,
- Hydroxychloroquine: main AE is GI and rash
- Azathioprine: monitor for cytopenia
Non biologic DMARDs special recommendations

- Screen for viral hepatitis and baseline chest x-ray prior to start methotrexate and leflunomide
- Baseline and periodic eye exam for Hydroxychloroquine
- Check for TPMT genotype prior to starting azathioprine in African-Americans
## Biologic DMARDs

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<thead>
<tr>
<th>Biologic agents</th>
<th>target</th>
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<tr>
<td>Anakinra</td>
<td>IL-1 B receptor</td>
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<tr>
<td>Etanercept, adalimumab, infliximab, certolizumab, golimumab,</td>
<td>TNF-alpha</td>
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<tr>
<td>Abatacept</td>
<td>T-Cell costimulation</td>
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<tr>
<td>Rituximab</td>
<td>CD-20+ B cells</td>
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<tr>
<td>Tocilizumab, sarilumab</td>
<td>IL-6 receptor</td>
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<tr>
<td>Tofacitinib, Baricitinib</td>
<td>JAK</td>
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Special considerations for biologics

- Screen for TB in all but rituximab
- Vaccinate for herpes zoster prior to JAK inhibitors
- Screen for hyperlipidemia in JAK inhibitors and IL-6 inhibitors
- Avoid JAK inhibitors and interleukin-6 inhibitors in patients with history of diverticulitis and H/O perforated intestines
- Watch for infections including severe infections. The risk is increased but low.
- Avoid in malignancy except for rituximab
- CHF, demyelinating dz and TNFi
- Avoid JAKi in pts with prior history of DVT
RA

Poor prognostic factors

- Functional limitation
- Extraarticular disease
- Rheumatoid factor positivity or presence of anticyclic citrullinated peptide (CCP) antibodies
- Bony erosions documented radiographically
Early RA treatment approach
2012 ACR recommendation, Copied from MKSAP17
Established RA treatment approach

2012 ACR RECOMMENDATIONS. Copied from ACP/MKSAP 17
Treat to target treatment goals

- Remission
- Reduce inflammation
- Decrease/prevent deformities
- Maintain function
- Decrease pain
- Improve quality of life
Treat to target

- It is important to follow disease activity and physical function measures to guide treatment options:
  - RAPID-3
  - CDAI
  - DAS28-ESR
  - DAS28-CRP
  - SDAI
  - HAQ-DI
  - ACR 20, 50, 70
  - PGA,
  - LABS
  - IMAGING
TICORA Trial

Introduction and Goals

- Developed to determine whether long term tight control was possible and if it had any benefit
- Determine cost efficiency of tight control
- Early treatment already known to improve outcomes
- Primary outcomes:
  - Decreased DAS
  - Increased proportion of good outcomes
- Secondary outcome: proportion resulting in remission
Patients and Methods

- Single blind randomized controlled trial
- 111 patients between 18-75 included with active RA (DAS>2.4) for less than 5 years
- Excluded patients previously on combined DMARDs, liver disease, hematological disease
- Blinded assessments by rheumatologists and radiologists

**Group 1: intensive care:**
- monthly evaluation by rheumatologist with DAS
- injections of appropriate swollen joints, and given IM steroids if no injections given first 3 months
- escalation of treatment if DAS still > 2.4

**Group 2: routine care:**
- evaluated every three month
- no specific scoring system
- DMARDs for synovitis
- escalation of therapy for worsening disease
Results and conclusions

- **Primary outcomes:**
  - Decreased DAS
    - Occurred in both, but consistently greater in intensive treatment group
  - Patients with good response
    - Intensive group has better response as measured by EULAR and ACR 70
  - Radiologic review shows less bony erosion in intensive group
  - Overall cost better with intensive group, but not to hospital or community

- **Conclusions:**
  - Tight control possible
  - Intensive control results in improvement of disease activity, radiographic disease progression, physical function and QOL
  - Tight control likely cost effective
BeSt Trial

Introduction

- Primary outcome: functional ability
  - HAQ
  - Yearly radiological joint damage on Sharp-van der Heijde score using blinded readers
- DAS steered treatment adjustments
- Clear treatment target
- Possible benefits of long term treatment to target
Methods

- Multicenter, randomized, single blind trial
- Targeted treatment and tight control
- Over 500 patients with 6 inflamed joints and high ESR or patient assessment indicating high disease activity
- Other DMARDs and prednisone added as needed with infliximab as secondary treatment
- Evaluation of patients every 3 months for DAS measurement and monitoring for toxicity
- DAS >2.4 led to treatment alterations
- DAS<2.4 for 6 months, tapering of therapy and in year three, discontinuation of last DMARD if down to monotherapy
Results and Conclusions

- Mean initial DAS 4.4
- Mean initial HAQ score 1.4
- Earlier and more frequent complete discontinuation of infliximab in patients in group 4, who had started on infliximab at initiation of study
- Early Combination treatment reduces symptoms and improves function and radiological progression

**Group 1 & 2**

Initial monotherapy
17%, 19% with DAS <2.4 respectively

**Group 3 & 4**

Initial combination therapy
DAS<2.4 at 3 months in 55%, 47% respectively
earlier remission
fewer treatment adjustments
Decreased radiologic progression at year 5
Vaccinations

Prevnar 13
Pneumovac 23
Flu shot
Herpes zoster

In general, all vaccinations are permitted with non-biologic DMARD’s

Live vaccinations are not permitted with biologic DMARD’s
RA CASES FROM MY PRACTICE
RA
summary

- Rheumatoid arthritis is a common and disabling disease
- Early diagnosis and treatment are important
- Treat to target has shown to improve the outcome of RA patients
- Recognize and manage comorbidities