Case Studies in Rheumatology

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Introduction to Rheumatoid Arthritis

Rheumatic Diseases

- Inflammatory
- Monoarticular: Septic arthritis (leg drainage, TB), Crystal arthropathy (gout, pseudogout)
- Polyarticular: Acute - SLE, RA (Symmetrical - Rheumatic, Systemic - SS)
- Spinal: Acute - Spondylitis

Non-inflammatory
- Monoarticular: Acute - Fractures, Sports Injuries
- Polyarticular: Fibromyalgia
- Spinal: Acute - Slipped disc
Rheumatoid Arthritis

- Teaching Plan
  - Background/Pathophysiology
  - Clinical Features
  - Treatment
    - DMARDs
    - NSAIDs
    - Steroids
    - Anti TNF, New and Future Treatments

RA - What is it?

- Chronic, systemic inflammatory disease, characterised by symmetrical joint involvement which is typically erosive/destructive

1987 ARC criteria for rheumatoid arthritis

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Requirement</th>
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<tbody>
<tr>
<td>Morning stiffness</td>
<td>&gt;1hr, &gt; 6 weeks</td>
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<tr>
<td>Arthritis of at least three areas</td>
<td>Soft tissue swelling or exudation lasting &gt; 6 weeks</td>
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<tr>
<td>Arthritis of hand joints</td>
<td>Wrist, metacarpophalangeal joints or proximal interphalangeal joints lasting &gt; 6 weeks</td>
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<tr>
<td>Symmetrical arthritis</td>
<td>At least one area, lasting &gt; 6 weeks</td>
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<tr>
<td>Rheumatoid nodules</td>
<td>As observed by a physician</td>
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<tr>
<td>Serum rheumatoid factor</td>
<td>By a method +ve in &lt; 5% controls</td>
</tr>
<tr>
<td>Radiographic changes</td>
<td>As on anteroposterior films of hands and wrists</td>
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Rheumatoid Arthritis

- Medieval times - Term first coined by Garrod (1859)
- Incidence - Western countries 1-3%
- Prevalence - 0.5-1% of population
- Female:Male - 3:1
- Age 30-50

RA - Aetiology

- Unknown
- Genetic
  - Polygenic. 30% identical twin concordance, 5% non-identical
  - 'Shared epitope' 'DR4-DR1' in 90%
- Hormonal

RA - Pathophysiology

- Activation of immune system
- Immunological pathways intersect
- Joint destruction
Cytokines

- Cytokines are local messenger and signalling molecules.
- Involved in development of the immune system (T cells and B cells), cell growth and differentiation, repair mechanisms and the inflammatory cascade.
- May be pro-inflammatory or anti-inflammatory.

Cytokines in Inflammation

**Pro-inflammatory**
- TNFα
- IL-1
- IL-6
- LIF
- LTα
- Chemokines

**Anti-inflammatory**
- IL-4
- IL-10
- IL-1Ra
- sIL-1R
- TGFβ
- sTNFR

Cytokines in Inflammation

- TNFα
- IL-1
- sTNFR
- IL-10
- IL-1Ra

Pro-inflammatory  Anti-inflammatory
RA - Pathology of Joints

- synovial lining increased
- T cells in dermis, especially CD4+; macrophages also
- synovium vascular
- many of the cells of all types activated, with increased production of cytokines and their receptors

Rheumatoid Arthritis

- Rheumatoid Factor - anti-IgG (Fc fragment)
  - Antibody can be IgM/IgG/IgA
    - Agglutination test (Latex/SCAT)
      - IgM RhF = seropositive disease
    - RIA/ELISA
      - IgG RhF may detect sero-negative disease

Rheumatoid Arthritis

- Rheumatoid Factors
  - Normal - 4%
  - CTD (often high titre 1/160+)
    - RA 70-80%
    - Sjogren's 75-100%
    - RA + sicca 100%
    - SLE 24-40%
    - Scleroderma 5-10%
    - Polyarteritis nodosa 0-5%
    - Dermatomyositis 0-5%
Rheumatoid Factor
Chronic infections (usually low titre)
- Syphilis
- Leprosy 50%
- Bacterial endocarditis 25%
- Pulmonary TB 5-20%
- Visceral larva migrans

Other immunological conditions
- Autoimmune liver disease
- Sarcoidosis
- Paraneoplastic
- Mixed cryoglobulinaemia
- Transplant recipients

Miscellaneous
- Relatives
- Increasing age

Rheumatoid Arthritis - Onset
- Acute
- Insidious
- Palindromic
- Systemic
- Polymyalgic
- Mono/oligoarticular

RA - Symptoms
- Polyarthritis
- Fatigue
- Diffuse musculoskeletal pain
- Swelling
- Morning stiffness
- Functional loss
**RA - Signs**

- Joints hot/swollen, tender to touch
- Anaemia
- Rh factor
- ESR/CRP
- Deformity and instability in joints
- Peri-articular features
- Non-articular formation

**Rheumatoid Arthritis**

- **Clinical Features**
  - Articular - symmetrical polyarthritis
    - Hands MCP, PIP, Wrists
    - Feet
    - Knees
    - Elbows
    - Ankles
    - Shoulders
    - Cervical spine
    - Temporomandibular joints
    - Cricoarytenoid joints (hoarseness)
    - Stapedius (Deafness)

**Rheumatoid Arthritis - Radiology**

**Early**

- soft tissue swelling
- juxta-articular osteoporosis
- joint space narrowing (cartilage loss)
- erosions (marginal)

**Late**

- bone and joint destruction
- subluxation
RA - Extra-articular Manifestations

• **Systemic**
  - malaise, fever, weight loss, myalgia
  - anaemia
    - Drugs
    - Disease activity
    - Felty's Syndrome
    - Haemolysis

• **Skin**
  - Cutaneous vasculitis
  - Rheumatoid nodules
  - Drug rashes
  - Palmar erythema
  - Skin atrophy

Extra-articular features

• **Local**
  - longstanding and severe cases
  - nodules in areas susceptible to trauma: eg elbows - palisade of macrophages surrounded by fibrous tissue

• **Systemic**
  - elevations of acute phase proteins. IL-6 may be responsible
  - vasculitis
  - serositis (eg pericarditis, pleurisy)
  - Felty's syndrome

Extra-articular features

• **Eyes**
  - Keratoconjunctivitis sicca (Sjogren's syndrome)
  - Scleritis/episcleritis
  - Scleromalacia perforans

• **Lungs**
  - Nodules - granulomas
  - Pleurisy/pleural effusions
  - Interstitial fibrosis
  - Caplan's syndrome
  - Obliterative bronchiolitis
  - Recurrent infections
**Extra-articular features**

- **Heart**
  - Pericarditis
  - Cardiomyopathy
  - Nodules (conduction/valvular defects)
  - Accelerated atherosclerosis

- **CNS**
  - Peripheral neuropathy - sensory, sensorimotor, mononeuritis multiplex
  - Autonomic neuropathy
  - Cervical myelopathy (atlanto-axial subluxation)
  - Cervical nerve root syndromes

**Extra-articular features**

- **Kidney**
  - Amyloid
  - Drug-related diseases
    - analgesic nephropathy, glomerulonephritis

- **GI**
  - Hepatosplenomegaly (Felty's /amyloid)
  - Abnormal LFTs
  - Drug-related disorders
    - gastric ulceration, intestinal ulceration, abnormal LFTs

**RA - Investigations**

- Anaemia
- WCC
- Platelets
- ESR
- CRP
- Rheumatoid factor
- LFTs
- Radiology
- Antinuclear antibodies
RA - Anaemia

• Serum iron decreased
• Serum ferritin normal or increased
• TIBC decreased

RA - When disease is active...

• Hb may fall
• WCC maybe increased
• Platelets maybe increased
• ESR, CRP increased
• Alkaline phosphatase increased

RA - Poor Prognosis

• Older onset
• Female
• Greater number of joints
• Uncontrolled polyarthritis
• Structural damage/deformity
• Functional disability
• Extra-articular features
• Psychosocial problems
• Rheumatoid factor
• (HLA-DR4/DR1 'shared epitope')
RA - When is it in remission?

- Morning stiffness <15 minutes
- No joint pain
- No fatigue
- No joint tenderness/pain on motion
- No soft tissue swelling
- ESR <30mm/hr (female)
  <20mm/hr (male)

Prescribing for Rheumatoid Arthritis

Teaching Plan

- Rheumatoid Arthritis
  - Background/pathophysiology
  - Treatment
    - DMARDs
    - NSAIDs
    - Steroids
    - New/future treatments
RA - Treatment Goals

- Relieve pain
- Prevent deformity
- Maintain normal function

- Education
- Exercise
- Physiotherapy
- Occupational therapy
- Dietary advice
- Pharmacotherapy
- Surgery

RA - Pharmacological Treatments

- ‘Pyramid’ approach reversed
- DMARDs commenced EARLY

- Disease modifying anti-rheumatic drugs (DMARDs)
  - slow joint destruction
  - reduce disability
  - reduce mortality

DMARDs

- Auranofin
- Azathioprine
- Ciclosporin
- Cyclophosphamide
- Hydroxychloroquine
- Leflunomide
- Methotrexate
- Mycophenolate mofetil
- Penicillamine
- Sulfasalazine
- Sodium Aurothiomalate (GOLD)
DMARDs - Methotrexate

- **Dose**
  - 7.5-30mg per week (target 15mg/week)

- **Response**
  - 3-12 weeks

**Side effects**
- nausea, diarrhoea
- oral ulceration
- mild alopecia
- bone marrow suppression
- alveolitis, interstitial pneumonitis
- hepatic fibrosis, cirrhosis
- teratogenic
- oligospermia

**Monitoring**
- Before treatment
  - FBC, U&Es, LFTs, urinalysis, chest X-ray, weight, alcohol intake
- During treatment
  - FBC every 2/52 for 2/12, then 1/12
  - LFTs every 1/12
  - U&Es every 6/12
  - [www.rheumatology.org.uk/guidelines/clinicalguidelines](http://www.rheumatology.org.uk/guidelines/clinicalguidelines)
“Towards the safer use of oral methotrexate”

- NPSA alert - 29th July 2004 (www.npsa.nhs.uk)

What is the role of folate?

- Folate deficiency is a risk factor for methotrexate toxicity
- 5mg ONCE weekly
- Not taken on same day as methotrexate
- No side effects and inexpensive (2p/week)
- ? Reduced cardiac risk

DMARDs - Sulfasalazine

- Dose - 500 mg od increase to 1g bd
- Response within 4-8 weeks
DMARDs - Sulfasalazine

- Side effects
  - nausea, abdo discomfort, headache
  - rash, allergic reaction, hepatitis
  - haemolytic anaemia, pancytopenia
  - macrocytosis, neutropenia
  - pulm.eosinophilia
  - oligospermia
  - renal changes
  - yellow/brown discoloration of urine/lenses

DMARDs - Sulfasalazine

- Monitoring
  - FBC, LFTs every 3/52 for 3/12 then....
  - FBC every 6/52 until 6/12 then every 3/12
  - LFTs every 6/12 after 3/12
  - www.rheumatology.org.uk/guidelines/clinicalguidelines

DMARDs - Gold

- Dose
  - im 50 mg weekly
    50mg 2/52
    50mg 4/52
  - oral 6mg-9mg od

- Response 10-16 weeks (im)
  3 months (oral)
DMARDs - Gold

- Side effects
  - rash
  - stomatitis/oral ulcers
  - vasomotor reactions
  - proteinuria
  - thrombocytopenia
  - leucopenia
  - pancytopenia
  - gold lung
  - diarrhoea

DMARDs - Gold

- Monitoring
  - Before treatment
    - FBC, U&Es, LFTs, urinalysis
  - Before each injection
    - skin, mouth
  - During treatment
    - FBC, urinalysis
  - Annually
    - chest X-ray

Leflunomide

- Binds to key enzyme involved in synthesis of pyrimidines
- Lf 100mg od for 3/7; Ml 20mg od
- Effect approx. 4 weeks
- Efficacy similar to MTX & SSA
- Adverse effects
  - pruritus, rash, GI, weight loss, alopecia
  - increase LFTs, hypertension
- C/I - pregnancy
- C/I - pregnancy
DMARDs - Leflunomide

- Monitoring
  - Before treatment
    • FBC, U&Es, LFTs, blood pressure
  - During treatment
    • FBC every 2/52 for 6/12, then 2/12
    • LFTs and BP every 1/12 for 6/12, then 2/12

www.rheumatology.org.uk/guidelines/clinicalguidelines

Combination Therapy

- MTX & SSA
- MTX, SSA & antimalarial drugs
- MTX & Ciclosporin
- MTX & Leflunomide

❓ Toxicity

Counselling of DMARDs

- Not a painkiller
- Take regularly
- Delayed onset of action
- Potential side effects & what to do about them
- Importance of monitoring
- ARC leaflets
Aims of Clinic

- To monitor the acceptability, efficacy and toxicity of disease modifying anti-rheumatic drugs (DMARDs)
- Support the patient by providing any additional drug information required

Type of service

- Hospital based rheumatology drug monitoring clinic
- Staffed by pharmacists, supported by rheumatologists and a specialist nurse

Role of Service

- Accept appropriate referrals for monitoring and dose adjustments of DMARDs
- Monitor and dose adjust DMARDs in accordance with agreed rheumatology protocols
- Educate and inform the patients regarding their DMARD therapy
- Maintain documentation
- Develop and update rheumatology shared care protocols (SCPs)
**Shared Care/Near Patient Testing (NPT)**

- Drugs that require a complex level of monitoring which is likely to exceed the expected expertise of the prescriber.
- NPT relates to drugs on the shared care list initially requiring a complex level of monitoring which is likely to exceed the expected expertise of the prescriber.
- Nationally-agreed list of drugs – GPs may monitor via NES or LES.

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**Which drugs are suitable for Shared Care/NPT?**

- Specialist determines whether drug suitable via MTAC and Shared Care sub-committee.
- Shared Care Protocol (SCP) developed.

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**Shared Care and NPT Rheumatology Drugs**

Cardiff & Vale NHS Trust (January 2006)

- Auranofin \( \text{SC/NES} \)
- Azathioprine \( \text{SC} \)
- Ciclosporin \( \text{SC/NES} \)
- Hydroxychloroquine \( \text{SC} \)
- Leflunomide \( \text{SC/LES} \)
- Methotrexate \( \text{SC/NES} \)
- Mycophenolate \( \text{SC} \)
- Penicillamine \( \text{SC/NES} \)
- Sodium Aurothiomalate \( \text{SC/NES} \)
- Sulfasalazine \( \text{SC/NES} \)

SC - Shared Care.
NES - National enhanced service.
LES - Local enhanced service.
Teaching Plan

• RA
  - Background/pathophysiology
  - Treatment
    • DMARDs
    • NSAIDs
    • Steroids
    • New/future treatments

Treatment - NSAIDs

• Efficacy
  - relief of morning stiffness
  - relief of joint swelling and tenderness
  - ESR & CRP decreased

• Monitoring
  - FBC, plasma urea & creatinine
  - Side effects

NSAIDs - Side effects

• Gastrointestinal
• Renal
• Hypersensitivity reactions
• CNS
• Blood dyscrasias
• ↑BP/worsening CCF
• Liver
Membrane Phospholipids

Arachidonic Acid

Cyclooxygenase-1
Housekeeping gene

Cyclooxygenase-2
Inflammatory gene

Phospholipase A2
Lipoxygenase

GI mucosal integrity
Renal function
Platelet aggregation (Thromboxane)

NSAIDs

Mitogenesis and growth
Regulation female reproduction
Bone formation
Renal function
Prostacyclin (blood thinning)

NSAIDs - GI Side effects

- Age
- History of ulcer
- Timing
- Type of NSAID
- Dose
- Sex
- Steroids/warfarin
- Smoking
- H pylori?
- Alcohol?

NSAIDs - Prophylaxis

- H₂ antagonists
- Misoprostol
- Proton pump inhibitors
Current Recommendations

- Dyspepsia
  - H\textsubscript{2} antagonist
  - PPI
- Active GDU - NSAID discontinued
  - H\textsubscript{2} antagonist
  - PPI
- Active GDU - NSAID continued
  - PPI
- Prophylaxis
  - Misoprostol
  - PPI


COX-2 Inhibitors

- COX-2 preferential
  - meloxicam (Mobic\textsuperscript{®})
  - etodolac (Lodine\textsuperscript{®})
- COX-2 selective
  - celecoxib (Celebrex\textsuperscript{®})
  - etoricoxib (Arcoxia \textsuperscript{®})
  - parecoxib (Dynastat\textsuperscript{®})
  - lumiracoxib (Prexige\textsuperscript{®})
Selective COX-2 Inhibitors Updated Safety Report
(February 2005)

Class effect

Increased risk of thrombotic events
- MI/Stroke
Dose/Duration ↑ risk
Etoricoxib - ↑ BP
Valdecoxib/Parecoxib - skin reactions

COX-2 Inhibitors
New advice for prescribers (CSM - August 2005)

• Switch patients with history of IHD or CVD
• In all patients - consider alternative treatments (individual risk/benefit assessment)
• Not with low dose ASPIRIN
• Use lowest effective dose for shortest duration

Teaching Plan

• RA
  - Background/pathophysiology
  - Treatment
    • DMARDs
    • NSAIDs
    • Steroids
    • New/future treatments
Role of Corticosteroids in RA

- Parenteral
  - Intra-articular (specific joint)
  - IM/IV (flare)
- Oral administration
  - 7.5mg/day effective dose

Teaching Plan

- RA
  - Background/pathophysiology
  - Treatment
    - DMARDs
    - NSAIDs
    - Steroids
    - New/future treatments

Cytokines in Inflammation

<table>
<thead>
<tr>
<th>Pro-inflammatory</th>
<th>Anti-inflammatory</th>
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<tbody>
<tr>
<td>TNFα</td>
<td>IL-4</td>
</tr>
<tr>
<td>IL-1</td>
<td>IL-10</td>
</tr>
<tr>
<td>IL-6</td>
<td>IL-1Ra</td>
</tr>
<tr>
<td>LIF</td>
<td>sIL-1R</td>
</tr>
<tr>
<td>LT α</td>
<td>TGFβ</td>
</tr>
<tr>
<td>Chemokines</td>
<td>sTNFR</td>
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Cytokines in Inflammation

**Pro-inflammatory**
- TNFα
- IL-1
- sTNFR

**Anti-inflammatory**
- IL-10
- IL-1Ra

New Treatments

- **Anti-cytokine therapy**
  - Soluble TNFα receptor - Etanercept (Enbrel)
    - twice weekly sc injections; 25mg dose (0.4mg/kg child)
    - once weekly; 50mg dose
  - Anti-TNFα antibodies - Infliximab (Remicade)
    - 3mg/kg dose; infusion; Md every 8 weeks
    - methotrexate co-prescribed to prevent formation of infliximab antibodies
  - Anti-TNFα antibodies - Adalimumab
    - human immunoglobulins
    - 40mg sc every 2 weeks

Adverse effects

- Infection
- Malignant disease
- Injection site/Infusion reactions
- Immune/Autoimmune responses
- Demyelinating syndromes
- Heart failure
NICE guidance (March 2002) - Etanercept and Infliximab

- RA patients who have failed to respond to at least 2 DMARDs (MTX)
- BSR guidelines (April 2001)
- Infliximab + MTX
- No response in 3/12 → WITHDRAW
- Biologics registry

Anti-TNF - monitoring

- Signs of anaphylaxis
- FBC
  - platelets/WCC
- Malignancy
- Pregnancy
- Infections (TB/PCP/thrush)
- Response - DAS scores (withdraw if >3.2)

What else is there?

- Mycophenolate - patient education (PIL)
- Rituximab - anti-B cell therapy
  - licensed for NHL initially (now also in RA)
  - 2 infusions 2 weeks apart
- Abatacept - anti-T cell therapy
  - not licensed in the UK YET
- Anakinra - IL-1 receptor antagonist