Rheumatology for GP Trainees: Inflammatory Arthritides (RA Including Early Recognition and Pharmacotherapeutics)

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Inflammatory Arthritis

- **Rheumatoid Arthritis (RA):**
  - Seropositive RA (70%)
  - Seronegative RA (30%)

- **Seronegative Spondyloarthropathies (SpA):**
  - Ankylosing Spondylitis (AS)
  - Psoriatic Arthritis (PsA)
  - Reactive Arthritis
  - Enteropathic Arthritis
  - Undifferentiated SpA
Rheumatoid Arthritis

- A general practice covers a population of 100,000 patients. How many patients with RA would be expected in this population?
  - A: 5,000
  - B: 2,500
  - C: 1,000
  - D: 500
  - E: 100
Rheumatoid Arthritis

- A general practice covers a population of 100,000 patients. How many patients with RA would be expected in this population?

- A: 5,000
- B: 2,500
- C: 1,000
- D: 500
- E: 100
Rheumatoid Arthritis: Epidemiology

- Chronic, multisystem autoimmune inflammatory disease of unknown aetiology, characterised by a symmetrical inflammatory polyarthropathy and extra-articular involvement.

- RA is the commonest inflammatory arthritis seen in primary and secondary care (0.8% prevalence).

- Female 3:1 Male.

- Peak age of onset 30 to 50.
Rheumatoid Arthritis: Aetiology

- Unknown aetiology
- RF (IgM antibodies against patients IgG)
- Anti-CCP antibodies (more specific than RF and of prognostic value)
- Genetics (incidence double in 1st degree relatives, dizygotic twins 5%, monozygotic twins 15%, HLA DR4)
- Environmental (infective trigger? cigarette smoking?, hormonal factors?)
Rheumatoid Arthritis: Pathogenesis

- Imbalance between pro-inflammatory cytokines (ie. TNF-α, IL-1, IL-6) and anti-inflammatory cytokines (ie. IL-10)

- Immune complexes accumulate in the joint and synovial tissue is infiltrated by lymphocytes and neutrophils

- Inflammation and proliferation of synovial tissue

- Cartilage and bony erosions

- Joint destruction and deformity
Rheumatoid Arthritis: Classification (not diagnosis)

- American College of Rheumatology (1987) **Classification** Criteria

<table>
<thead>
<tr>
<th>Morning stiffness</th>
<th>Morning stiffness lasting at least 1 hour (&gt;6 weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arthritis of ≥3 joint areas</td>
<td>Soft tissue swelling in at least 3 joints (&gt; 6 weeks)</td>
</tr>
<tr>
<td>Arthritis of hand joints</td>
<td>Wrist, MCPJ or PIPJ swelling (&gt;6 weeks)</td>
</tr>
<tr>
<td>Symmetrical arthritis</td>
<td>Simultaneous bilateral joint involvement (&gt;6 weeks)</td>
</tr>
<tr>
<td>Rheumatoid nodules</td>
<td>Subcutaneous nodules</td>
</tr>
<tr>
<td>Serum rheumatoid factor</td>
<td>Positive RF</td>
</tr>
<tr>
<td>Radiographic changes</td>
<td>Hand and wrist radiographic changes typical of RA</td>
</tr>
</tbody>
</table>
Rheumatoid Arthritis: Classification (not diagnosis)

RF RISES

Rheumatoid factor positive
Finger (MCPJ/PIPJ) or wrist swelling (>6 weeks)

Rheumatoid nodules
Involvement of 3 or more joints (>6 weeks)
Stiffness in the early morning for more than 1 hour (>6 weeks)
Erosions or peri-articular osteoporosis on X-rays
Symmetric arthritis (>6 weeks)
# 2010 ACR/EULAR Classification Criteria for RA

## Joint Distribution (0-5)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<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 (large joints not counted)</td>
<td>2</td>
</tr>
<tr>
<td>4-10 small joints (large joints not counted)</td>
<td>3</td>
</tr>
<tr>
<td>&gt;10 joints (at least one small joint)</td>
<td>5</td>
</tr>
</tbody>
</table>

## Serology (0-3)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<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>
</tbody>
</table>

## Symptom Duration (0-1)

<table>
<thead>
<tr>
<th>Duration</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;6 weeks</td>
<td>0</td>
</tr>
<tr>
<td>≥6 weeks</td>
<td>1</td>
</tr>
</tbody>
</table>

## Acute Phase Reactants (0-1)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal CRP AND normal ESR</td>
<td>0</td>
</tr>
<tr>
<td>Abnormal CRP OR abnormal ESR</td>
<td>1</td>
</tr>
</tbody>
</table>

\[ \geq 6 = \text{definite RA} \]

What if the score is <6?

Patient might fulfill the criteria…

→ **Prospectively** over time (cumulatively)

→ **Retrospectively** if data on all four domains have been adequately recorded in the past
BOUTONNIERE AND SWAN-NECK DEFORMITIES

Boutonnière deformity

Swan-neck deformity

Lateral band, volar to axis of motion

DIP flexion
PIP extension

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RA: X-ray changes

- Early changes (soft tissue swelling, juxta-articular osteoporosis)
- Intermediate changes (joint space narrowing, erosions)
- Late changes (bone and joint destruction, subluxation, secondary OA)
RA: Extra-articular features

- Rheumatoid disease
- 30% of patients (NB. fatigue) (mostly seropositive)
- Rheumatoid nodules most common extra-articular feature
- Cutaneous (palmar erythema, Raynaud’s, vasculitis)
RA: Extra-articular features

- Ophthalmic (secondary Sjögren’s, episcleritis, scleritis, scleromalacia perforans)

- Cardiac (pericarditis, myocarditis, coronary vasculitis, CV disease = DM)

- Respiratory (bronchiectasis, pleural effusions, fibrosis, rheumatoid nodules, pneumonitis)
RA: Extra-articular features

- Renal (secondary amyloidosis, NSAIDs – interstitial nephropathy)
- Neurological (carpal tunnel, cervical myelopathy, symmetrical peripheral neuropathy, mononeuritis)
- Lymphoreticular (Felty’s, lymphoma)
- Anaemia (chronic disease, NSAIDs, pernicious anaemia, AIHA, Felty’s, DMARDs)
RA: Management

- History, Examination, Investigations
- Pain
- Function
- Modify disease process
- MDT (sometimes even orthopaedic surgeons can be helpful)
DMARDs

• Drug that modifies underlying disease process and inflammation:
  ▫ Slow onset of action
  ▫ Reduction in acute phase response
  ▫ Improvement in function (HAQ)
  ▫ Slowing rate of radiological progression

• Non-Biologic DMARDs (MTX, SZS, LEF)
• Biologic DMARDs
A middle-aged man with longstanding RA presents with a red, swollen, hot right knee. His temperature is 39.2 degrees. What is the immediate management?

- A: IV Flucloxacillin and Benzylpenicillin
- B: Blood cultures
- C: Joint aspiration, microscopy and culture
- D: Oral prednisolone and physiotherapy
- E: Commence methotrexate
Rheumatoid Arthritis: Complications

- A middle-aged man with longstanding RA presents with a red, swollen, hot right knee. His temperature is 39.2 degrees. What is the immediate management?
  
  - A: IV Flucloxacillin and Benzylpenicillin
  - B: Blood cultures
  - C: Joint aspiration, microscopy and culture
  - D: Oral prednisolone and physiotherapy
  - E: Commence methotrexate

- *Arthritis begets Arthritis* (ie. Septic Arthritis, Osteoarthritis)
Remember to think about, look for and don’t miss septic arthritis
Rheumatoid Arthritis

Early Inflammatory Arthritis (EIA/UA) and the Importance of Early Recognition
Rheumatoid Arthritis: Early Inflammatory Arthritis and the Importance of Early Recognition

- Problems in Arthritis
  - Perception: Nothing can be done
  - Priority: Arthritis is non life-threatening (cancer, heart disease, not part of NSF)
  - “Presents late but irrelevant as even if can be seen early, there is no accurate diagnosis and no effective therapy”
Rheumatoid Arthritis:  
Early Inflammatory Arthritis and the Importance of Early Recognition

- Problems in Arthritis
  - Perception: Nothing can be done
  - Priority: Arthritis is non life-threatening (cancer, heart disease, not part of NSF)
  - “Presents late but irrelevant as even if can be seen early, there is no accurate diagnosis and no effective therapy”

- 1 in 5 of population has some form of arthritis
- 72% of people with arthritis meet legal definition of disability
- 20% of GP consultations are arthritis related (25% are dissatisfied with treatment)
Rheumatoid Arthritis

- Chronic inflammatory disease of unknown etiology
- Persistent inflammation in predisposed individual leads to chronicity
- Fluctuating clinical course characterized by
  - Progressive destruction of synovial joints with loss of cartilage and bone
  - Damaged ligaments and tendons
  - Loss of physical function and quality of life
  - Premature death
Rheumatoid Arthritis: Economic Burden

- In the UK, average RA outpatient cost/case/year was £798 in 1997

- RA costs average:
  - 49% of cost of cancer
  - 68% of cost of stroke
  - 82% of cost of coronary heart disease

- Indirect costs
  - 3 to 4 times higher than direct costs
  - Lifetime costs £500,000
Rheumatoid Arthritis

- Who gets it?
Rheumatoid Arthritis: Social and Psychological

- Moderate disability within 2 years of diagnosis, severe by 10 years (relentless spread, analogous to malignancy)

- Inability to work within 10 years of onset
  - Approximately 50% of RA patients

- Feelings of helplessness and other psychological distress

- Potential inability to carry out social role
Early Rheumatoid Arthritis

Established Rheumatoid Arthritis

Normal Knee Joint

Early IA: Definition

• ‘Early’ IA not well defined in the literature

• Moving target
  • Better diagnostic tests
  • Better understanding of the disease

• 10-15 years ago ?5+ years = early arthritis

• Currently ?3 to 6 months from onset of symptoms
Early IA

- Rheumatoid Arthritis vs Not Rheumatoid Arthritis
- Requires MTX vs Doesn’t Require MTX
The ‘Window of Opportunity’

- Damage occurs early
- Subclinical disease is common
- Remission is rare
- Inflammation $\times$ Time $= \text{DAMAGE}$
The ‘Window of Opportunity’

- Aggressive, early treatment prevents erosion
- DMARD treatment is not necessarily toxic
- Opportunity to “switch off” disease with newer therapies
- Remission is now becoming a realistic goal
Early RA
Normal X-ray
1 year
Inflammation x Time = Damage
Clinical Features of Early RA

- History
- Examination
- Laboratory tests
- Imaging
History:
Who do we want to see?
Early Arthritis Clinic?

• Polyarthropathy (may present as mono, oligo or polyarthropathy)

• Morning joint stiffness (>30 minutes, non-specific)

• Persistence (>6 /52)
Examination

• Joint tenderness and swelling
  ▫ MCPJ and MTPJ squeeze test (strong predictor of progression to RA)

• Symmetrical (but often not at presentation)
Have you got... The S Factor?

**Stiffness**
Early morning joint stiffness lasting over 30 minutes

**Swelling**
Persistent swelling of one joint or more, especially hand joints

**Squeezing**
Squeezing the joints is painful in inflammatory arthritis

For further information, please contact:

The National Rheumatoid Arthritis Society
Unit B4 Westacott Business Centre
Westacott Way, Littlewick Green
Maidenhead, SL6 3RT

Phone: 0845 458 3969
Free Helpline: 0800 298 7650
Email: enquiries@nras.org.uk
Web: www.nras.org.uk

This could be inflammatory arthritis
See your doctor now! Delay can cause long term disability
Investigations: Laboratory Tests

- Acute phase response (CRP, PV, ESR)

- RF
  - High titre associated with worse prognosis
  - False positives
    - Chronic disease, SjS, SLE, neoplasm, infection, smoking, cryoglobulinaemia, age

- Anti-CCP Ab (I would recommend NOT checking)
  - Highly specific
  - Associated with worse prognosis
Investigations: Imaging (Rheum OP)

- Erosions indicative but not specific (ie. gout, PsA, erosive OA)

- Erosions seldom occur within 1st year of symptoms

- MRI / US

- Diagnosis is clinical – don’t delay seeking specialist help by waiting for test results
Why the Delay?

• Patient developing symptoms and presenting to primary care?

• Primary care referring to secondary care?

• Being seen in primary care?

• Delay in secondary care initiating therapy?
Differential Diagnosis

- Self limiting viral/post-viral arthropathy
  - Parvovirus B19

- Crystal arthritis

- Connective tissue disease
  - Other symptoms
  - Urinalysis

- Seronegative SpA
  - Inflammatory back-pain, psoriasis, IBD, enthesitis, uveitis, gastroenteritis, urethritis
Rheumatoid arthritis

The management of rheumatoid arthritis in adults

Issue date: February 2009
1.1 Referral, diagnosis and investigations

1.1.1 Referral for specialist treatment

1.1.1.1 Refer for specialist opinion any person with suspected persistent synovitis of undetermined cause. Refer urgently if any of the following apply:

- the small joints of the hands or feet are affected
- more than one joint is affected
- there has been a delay of 3 months or longer between onset of symptoms and seeking medical advice.

1.1.1.2 Do not avoid referring urgently any person with suspected persistent synovitis of undetermined cause whose blood tests show a normal acute-phase response or negative rheumatoid factor.
Management

• Pain, Function, Disease Modification

• MDT approach essential

• Early pharmacological intervention has lasting effects on long-term outcome
  ▫ Combination therapy (COBRA)
  ▫ MTX (‘anchor’ drug)
  ▫ Role of steroids (initial, bridging, flares, co-morbidities)
  ▫ Biologics for non-responders
Disease-modifying and biological drugs

- In people with newly diagnosed active RA, offer a combination of disease-modifying anti-rheumatic drugs (DMARDs) (including methotrexate and at least one other DMARD, plus short-term glucocorticoids) as first-line treatment as soon as possible, ideally within 3 months of the onset of persistent symptoms.

- In people with newly diagnosed RA for whom combination DMARD therapy is not appropriate\(^1\), start DMARD monotherapy, placing greater emphasis on fast escalation to a clinically effective dose rather than on the choice of DMARD.

- In people with recent-onset RA receiving combination DMARD therapy and in whom sustained and satisfactory levels of disease control have been achieved, cautiously try to reduce drug doses to levels that still maintain disease control.
Summary: EIA and Importance of Early Recognition

- Identification, early referral and treatment of early inflammatory arthritis is crucial (clinical diagnosis)
- Primary care is key component to chain (where is delay?)
- With earlier identification and intervention, remission is now the goal
QAF

• Practices should produce a register of all patients aged 16 years and over with RA

• The percentage of patients with RA aged 30-84 years who have had a CV risk assessment using CVD risk assessment tool adjusted for RA in the preceding 15 months

• The percentage of patients aged 50-90 years with RA who have had an assessment of fracture risk using a risk assessment tool adjusted for RA in the preceding 27 months

• The percentage of patients with RA who have had a face to face annual review in the preceding 15 months
Biologic Therapies
Biologic Therapies: What Are They?

• Imbalance of pro-inflammatory and anti-inflammatory cytokines

• Biologic therapies are agents that target inflammatory cytokines and other cellular targets
  ▫ Monoclonal antibodies to TNF-α (ie. infliximab, adalimumab)
  ▫ TNF-α receptor antibodies (ie. etanercept)
  ▫ Receptor antagonists/blockers (ie. anakinra, tocilizumab)
  ▫ B-cell inhibitor (ie. rituximab)
  ▫ T-cell co-stimulator inhibitor (ie. abatacept)
Biologic Therapies: What Is Out There?

- **Anti-TNF Therapies:**
  - **Monoclonal Antibodies:**
    - Infliximab (Remicade) (Schering-Plough, MSD)
    - Adalimumab (Humira) (Abbott)
    - Certolizumab (Cimzia) (UCB)
    - Golimumab (Simponi) (Schering-Plough, MSD)
  - **TNF receptor Antibodies:**
    - Etanercept (Enbrel) (Pfeizer)
Biologic Therapies: What Is Out There?

- **CD-20 positive B-cell inhibitor**
  - **Rituximab (Mabthera)** (Roche)

- **IL-6 antagonist:**
  - **Tocilizumab (RoActemra)** (Chugai-Roche)

- **T-cell co-stimulator inhibitor**
  - **Abatacept (Orencia)** (Bristol-Myers-Squibb)
Biologic Therapies: What Is Out There?

- **Anti-TNF Therapies:**
  - **Monoclonal Antibodies:**
    - Infliximab
    - Adalimumab
    - Certolizumab
    - Golimumab
  - **TNF receptor:**
    - Etanercept
Biologic Therapies: What Is Out There?

Infliximab (Remicade)

- Chimeric (human/murine) IgG monoclonal antibody to TNF-α (first available TNF – FDA approval 1998)
- Intravenous infusion (3mg/kg in RA) over 1 hour
- Weeks 0, 2 and 6 and then 8 weekly (half-life 10 days)
- Prescribed in combination with MTX:
  - Combination therapy leads to better clinical outcomes
  - Prevention of antibody formation (chimeric)
Biologic Therapies: What Is Out There?

- **Anti-TNF Therapies:**
  - **Monoclonal Antibodies:**
    - Infliximab
    - Adalimumab
    - Certolizumab
    - Golimumab
  - **TNF receptor:**
    - Etanercept
Biologic Therapies: What Is Out There?
Adalimumab (Humira)

- Fully humanised monoclonal IgG anti-TNF-α antibody
- 40mg SC every other week (pre-filled pen) (half-life 2 weeks)
- Usually co-prescribed with MTX
Biologic Therapies: What Is Out There?

- **Anti-TNF Therapies:**
  - **Monoclonal Antibodies:**
    - Infliximab
    - Adalimumab
    - Certolizumab
    - Golimumab
  - **TNF receptor:**
    - Etanercept
Biologic Therapies: What Is Out There?

• Anti-TNF Therapies:
  ▫ Monoclonal Antibodies:
    • Infliximab
    • Adalimumab
    • Certolizumab
    • Golimumab
  ▫ TNF receptor:
    • Etanercept
Biologic Therapies: What Is Out There?
Etanercept (Enbrel)

- Fully humanised soluble TNF-α receptor antibody (binds to and blocks the action of TNF-α)
- 25mg SC twice a week (pre-filled pen) (half-life 3 days)
- Usually co-prescribed with MTX
Biologic Therapies: What Is Out There?

- **CD-20 positive B-cell inhibitor**
  - **Rituximab** (Chugai-Roche)

- **IL-6 antagonist**:
  - **Tocilizumab** (Chugai-Roche)

- **T-cell co-stimulator inhibitor**
  - **Abatacept** (Bristol-Myers-Squibb)
Biologic Therapies: What Is Out There?
Rituximab (MabThera)

- Chimeric (human/murine) anti-CD20 positive B-cell monoclonal antibody
- 2 x IV infusion (1g 2 weeks apart)
- Course repeated when required (usually 6 months) (half life 21 days)
- Usually prescribed in combination with MTX
- Used in RA when patient has had an inadequate response or is intolerant to an anti-TNF-α agent (?seropositivity)
Biologic Therapies: What Is Out There?

- **CD-20 positive B-cell inhibitor**
  - *Rituximab* (Chugai-Roche)

- **IL-6 antagonist:**
  - *Tocilizumab* (Chugai-Roche)

- **T-cell co-stimulator inhibitor**
  - *Abatacept* (Bristol-Myers-Squibb)
Biologic Therapies: What Do We Use Them For?

- Rheumatoid Arthritis (RA)
- Psoriatic Arthritis (PsA)
- Ankylosing Spondylitis (AS)
Issue date: October 2007
Review date: September 2010

Adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis

Includes a review of technology appraisal guidance 36
Adalimumab, Etanercept & Infliximab for RA

- Adalimumab, etanercept and infliximab are treatment options for adults with RA who have the following characteristics:
  - Active RA (Disease Activity Score > 5.1) on at least two occasions, 1 month apart
  - Have failed or been intolerant to MTX and one other Disease-Modifying Anti-Rheumatic Drug (DMARD)

- TNF-α therapy should only be continued if there is an adequate response at 6 months following initiation of therapy (DAS28 improvement of ≥ 1.2 points)
Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor

NOTE: This guidance replaces NICE technology appraisal guidance 126 and 141 issued in August 2007 and April 2008 respectively. It also replaces the remaining recommendations in NICE technology appraisal guidance 36 issued in March 2002.

The appraisal of adalimumab and the review of the appraisals of etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis have resulted in changes in the guidance. Rituximab in combination with methotrexate is still recommended as an option for the treatment of adults with severe active rheumatoid arthritis who have had an inadequate response to, or have an intolerance of, other DMARDs, including at least one TNF inhibitor. Additional treatment options are now recommended for these adults if rituximab therapy is contraindicated or withdrawn because of an adverse event, specifically:
Patients With RA Who Fail Anti-TNF Therapy

- Rituximab
- Adalimumab, Etanercept, Infliximab
- Abatacept
- Tocilizumab
Etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis (review of technology appraisal guidance 104 and 125)

NOTE: This guidance replaces NICE technology appraisal guidance 104 issued in July 2006 and NICE technology appraisal guidance 125 issued in August 2007.

NICE reviews each piece of guidance it issues. This review and re-appraisal has resulted in an extension to the guidance:

- Etanercept, infliximab and adalimumab are all recommended for the treatment of active and progressive psoriatic arthritis, based on specific criteria. Treatment choice should be started with the least expensive drug (taking into account drug administration costs, required dose and product price per dose).

- The guidance recommends that treatment should be discontinued if people's disease does not show an adequate response on the Psoriatic Arthritis Response Criteria (PsARC) at 12 weeks. Healthcare professionals should also consider continuing treatment if people's skin disease has a Psoriasis Area and Severity Index (PASI) 75 response.
Adalimumab, Etanercept & Infliximab for PsA

- Adalimumab, etanercept, infliximab are recommended for the treatment of adults with PsA who have the following characteristics:
  - Active involvement of ≥ 3 joints
  - Inadequate response to at least 2 DMARDs
Adalimumab, etanercept and infliximab for ankylosing spondylitis

Guidance
1. Adalimumab or etanercept are recommended as treatment options for adults with severe active ankylosing spondylitis only if all of the following criteria are fulfilled.
   - The patient’s disease satisfies the modified New York criteria for diagnosis of ankylosing spondylitis.
   - There is confirmation of sustained active spinal disease, demonstrated by:
     - a score of at least 4 units on the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)
     - an increase in Bath Ankylosing Spondylitis Functional Index (BASFI) score by at least 1 unit
   - Where the BASDAI or spinal pain VAS score is not a clinically appropriate tool to inform a clinician’s conclusion on the presence of sustained active spinal disease because of a patient’s learning or other disabilities (for example, sensory impairments) or linguistic or other communication difficulties
   - Where it is not possible to administer the anti-TNF agent
   - Where the patient’s health status, measured by the Ankylosing Spondylitis Disease Activity Index (ASDAI), is not a clinically appropriate tool to inform a clinician’s conclusion on the presence of sustained active spinal disease because of a patient’s learning or other disabilities (for example, sensory impairments) or linguistic or other communication difficulties

These are:
Adalimumab & Etanercept for AS

- Adalimumab or etanercept are recommended as treatment options for adults with AS who fulfil the following characteristics:
  - Active spinal disease (BASDAI $\geq 4$ AND $\geq 4$ on spinal pain VAS, on 2 occasions at least 12 weeks apart)
  - Failed $\geq 2$ NSAIDs

- Response to treatment assessed at 12 weeks

- Adequate response is a reduction in BASDAI by $\geq 2$ units AND reduction of spinal pain VAS by $\geq 2$ units
Biologic Therapies: Any Questions?

- Do they work?
- How do you choose between biologics/anti-TNFs?
- How quickly do patients respond?
- Safety issues?
- Cost?
- What about pregnancy?
- What about if a patient needs surgery?
- Any other uses for biologics?
Do They Work?
CIMZIA® provides rapid and lasting results\(^1,7\)
- ACR response rates continued to increase up to week 12, lasting to week 52\(^1\)

\[\begin{align*}
\text{RAPID 1: Significant ACR Response at Week 12 Lasting to Week 52 (ITT pop.)}\, &\, ^1,8 \\
\end{align*}\]

\[\begin{align*}
\text{%} & \quad \text{Weeks} \\
0 & \quad 0 \\
20 & \quad 12 \\
40 & \quad 14 \\
60 & \quad 20 \\
{} & \quad 24 \\
{} & \quad 28 \\
{} & \quad 32 \\
{} & \quad 36 \\
{} & \quad 40 \\
{} & \quad 44 \\
{} & \quad 48 \\
{} & \quad 52 \\
\end{align*}\]

\([-\text{ACR20} - \text{ACR50} - \text{ACR70} - \text{CIMZIA 200 mg every 2 weeks + MTX (n=393)}]\)

\({}^1\) CIMZIA\(^*\) + MTX

\({}^1\) P<0.001 vs placebo (week 52 placebo responses: ACR20, 13%; ACR50, 8%; ACR70, 4%).\(^8\)
Do They Work?

- Anti-TNF-α therapy:
  - ACR20 – 60%
  - ACR50 – 40%
  - ACR70 – 20%

- ACR response (TJ, SJ, patient and clinician global assessments, pain, disability, inflammatory markers)
  - 1/3 remission, 1/3 good response, 1/3 poor response
How Do You Choose Between Biologics?

- Infliximab (IV, ↑TB, antibodies, cost)
- Adalimumab (SC, ?antibodies, monotherapy)
- Certolizumab (SC, 3 months free, ?faster response)
- Golimumab (SC, monthly)
- Etanercept (SC, twice a week, ↓half-life, monotherapy)
- Rituximab (slower response, IV, reaction, PML, ↓infection, ↓cost, seropositivity)
- Tocilizumab (novel mechanism of action, ?antibodies)
- Abatacept (slower response)
How Quickly Do Patients Respond?

- Anything between a few days and 6 months
- Usually assess at 3 months
- Certolizumab (?faster response)
- Rituximab (slower response)
- Abatacept (slower response)
Safety Issues?

- Infection
- Infusion reaction (rituximab)
- SC injection site reaction
- TB reactivation (infliximab)
- Lupus syndrome
- Demyelination, MS (anti-TNF therapy)
- Malignancy (BCC, lymphoma)
- PML (rituximab)
- Heart failure (grade III/IV and infliximab)
Cost?

- About £9,500 per year
- Infliximab (3mg/kg, infusion costs)
- Certolizumab (clever marketing)
- Rituximab (£7000/yr including infusion costs)
What About Pregnancy?

- No good evidence that anti-TNF therapy is unsafe
- No trial evidence that anti-TNF therapy is safe (and there won’t be)
- ?VACTERL
- A number of successful pregnancies
- Recommendation is that anti-TNF therapy is discontinued prior to conception (NICE, drug companies)
- Rituximab (B-cell depletion in neonate)
What If A Patient Needs Surgery?

- Little evidence in the literature regarding the perioperative use of biological therapies (lack of human study data)
- Concerns over infectious complications and delayed wound healing
- Small prospective controlled study (31 patients) in patients on anti-TNF therapy undergoing elective orthopaedic foot and ankle surgery showed no increase in infectious or healing complications

BSR guidelines suggest that anti-TNF therapy should be withheld for 2-4 weeks prior to any major surgical procedure (restart postoperatively if there is no evidence of infection and once wound healing is satisfactory)

The Perioperative Use of Disease Modifying and Biologic Therapies in Patients with Rheumatoid Arthritis Undergoing Elective Orthopedic Surgery

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educational objectives

As a result of reading this article, physicians should be able to:

1. Identify the current evidence in regards to perioperative use of disease modifying anti-rheumatic drugs (DMARDs) in orthopedic surgery.
Any Other Uses For Biologics?

- RA, PsA, AS
- JIA (Etanercept)
- SLE (Rituximab)
- ANCA-positive vasculitides (Rituximab)
- Auto-inflammatory syndromes (Anti-TNF, Anakinra, Tocilizumab)
- Inflammatory bowel disease (Adalimumab)
- Inflammatory eye disease (Infliximab)
- Psoriasis (Ustekinumab)