A FOCAL POINT LEARNING PROGRAMME

RHEUMATOID ARTHRITIS

BOOK 1
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CENTRE FOR PHARMACY
POSTGRADUATE EDUCATION
Design team
Pardeep Chera, chief pharmacy technician-interface, Derby Hospitals NHS Foundation Trust
Richard Copeland, head of clinical pharmacy services, Northumbria Healthcare NHS Foundation Trust
Helen Root, teacher practitioner, De Montfort University
Matthew Shaw, deputy director, CPPE
Ian Scott, lead clinical pharmacist, medicine, Pilgrim Hospital, Boston
Sharon Warren, tutor, Dudley and Sandwell
Rekha Williams, expert patient and joint head of communications, CPPE

CPPE programme developer
Karen Wragg, senior pharmacist, learning development

Reviewers
Richard Copeland, head of clinical pharmacy services, Northumbria Healthcare NHS Foundation Trust
Mark Thomas, lead clinical pharmacist, Gateshead Health NHS Foundation Trust

CPPE reviewers
Chris Cutts, director
Layla Fattah, pharmacist, learning development
Matthew Shaw, deputy director
Sharon Warren, tutor, Dudley and Sandwell

Piloted by
Sally Greensmith, tutor, West Surrey

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Learning with CPPE

The Centre for Pharmacy Postgraduate Education (CPPE) offers a wide range of learning opportunities for the pharmacy workforce. We are based in the University of Manchester’s School of Pharmacy and Pharmaceutical Sciences and are funded by the Department of Health to provide continuing education for practising pharmacists and pharmacy technicians providing NHS services in England. For further information about our learning portfolio, visit: http://www.cppe.ac.uk

We recognise that people have different levels of knowledge and not every CPPE programme is suitable for every pharmacist or pharmacy technician. We have created three categories of learning to cater for these differing needs:

- **CPPE 1** Core learning (limited expectation of prior knowledge)
- **CPPE 2** Application of knowledge (assumes prior learning)
- **CPPE 3** Supporting specialties (CPPE may not be the provider and will direct you to other appropriate learning providers).

This is a **CPPE 2** learning programme and assumes that you already have some knowledge of the topic area.

**Continuing professional development (CPD)** – You can use this *focal point* unit to support your CPD. Consider what your learning needs are in this area. Use your CPD record sheets to plan and record your learning.

**Programme guardians** – A programme guardian is a recognised expert in an area relevant to the content of a learning programme. They will review the programme every six months to ensure quality is maintained. We will post any alterations or further supporting materials that are needed as an update on our website. We recommend that you check for these updates if you are using a programme more than six months after its initial publication date.

**Feedback** – We hope you find this learning programme useful for your practice. Please help us to assess its value and effectiveness by visiting the *my CPPE record* page on our website. Alternatively, please email us at: feedback@cppe.ac.uk
About CPPE focal point programmes

We have developed focal point to give you short, clinically focused learning sessions. It will help you learn with your colleagues and improve the services you offer your patients. Each unit presents information and activities that are relevant for pharmacy professionals working in primary care and in the community. There are two types of learning event for you to choose between when using focal point units – you can either attend a CPPE tutor-led event or can learn as part of a CPPE ‘learning community’. Have a look at the CPPE website: http://www.cppe.ac.uk for more information about how to set up a learning community.

Reference sources for all the books, articles, reports and websites mentioned in the text can be found at the end of the programme. References are indicated in the text by a superscript number (like this 3).

This book gets you started. It provides key information to help you meet the learning objectives presented overleaf, but it also encourages you to identify your own learning needs. It then challenges you to relate what you have learnt to your own area of practice and professional development. We have included practice points and talking points to stimulate your thinking and we will refer to these again at the focal point event. Make sure you have studied these activities before your event.

You will receive Book 2 when you attend the focal point event. It uses a case study and ‘clinical vignettes’ to help you apply what you have learnt and includes a Directing change section that offers a framework to encourage you to make changes to improve your practice. We also include some suggested answers to the learning activities.

About this focal point unit on rheumatoid arthritis

In this unit we consider:

- how to recognise which patients are most likely to have rheumatoid arthritis (RA)
- the current approaches in the management of RA, both to modify progression of the disease and to treat pain and acute flares
- how to implement a holistic approach to anticipating and meeting the specific needs of RA patients using the whole pharmacy team.
### Learning objectives

You can meet the learning objectives that we identify here by reading the information that we provide and refer you to, undertaking the various activities that we suggest and putting what you have learnt into practice. We have split our learning objectives into appropriate sections. This should help you determine how to meet them. We have also linked the learning objectives in this programme to the General Level Framework (GLF) and the NHS Knowledge and Skills Framework (KSF) dimensions. We have suggested some competences, but you may be able to apply your learning to other aspects of these frameworks.

#### Moving into focus and Reading

<table>
<thead>
<tr>
<th>Objective</th>
<th>KSF</th>
<th>GLF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recognise the signs and symptoms of RA</td>
<td>HWB 7 Level 2</td>
<td>Cluster: Problem solving Competency: Knowledge</td>
</tr>
<tr>
<td>Discuss the management of pain in RA and treatment of acute flares</td>
<td>HWB 6 Level 2</td>
<td>Cluster: Delivery of patient care Competency: Need for the drug</td>
</tr>
<tr>
<td>Describe the current approaches to RA management to modify progression of the disease</td>
<td>HWB 7 Level 3</td>
<td>Cluster: Problem solving Competency: Use of guidelines</td>
</tr>
</tbody>
</table>

#### Practice points, talking points, case study and clinical vignettes

You’ll find these in this book and Book 2, and will work on them during the event.

<table>
<thead>
<tr>
<th>Objective</th>
<th>KSF</th>
<th>GLF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Review your current approach to supporting patients with RA and identify ways to help them in managing their disease</td>
<td>HWB 6 Level 3</td>
<td>Cluster: Delivery of patient care Competency: Medicines information and patient education</td>
</tr>
<tr>
<td>Provide advice on the review and optimisation of medicines in RA</td>
<td>HWB 7 Level 3</td>
<td>Cluster: Delivery of patient care Competencies: Drug-specific issues, selection of drug, selection of formulation and concentration and monitoring drug therapy</td>
</tr>
</tbody>
</table>
Directing change scenarios and follow-up activities

You will achieve practical outcomes after completing this unit, when you apply what you have learnt to your everyday practice. You will find advice in Book 2.

<table>
<thead>
<tr>
<th>Objective</th>
<th>KSF</th>
<th>GLF</th>
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</thead>
<tbody>
<tr>
<td>Implement a holistic approach to anticipating and meeting the specific needs of patients with RA, using the whole pharmacy team</td>
<td>Service improvement</td>
<td>Cluster: Management and organisation</td>
</tr>
<tr>
<td></td>
<td>Level 3</td>
<td>Competency: Service development</td>
</tr>
</tbody>
</table>
Useful resources

We have selected some resources that you can use when developing improved pharmacy services for people with RA.

Support for patients

Arthritis Care – http://www.arthritiscare.org.uk
Arthritis Care is a voluntary organisation working with, and for, all people with arthritis. It provides information and support on a range of issues related to living with arthritis and campaigns locally and nationally.

Children’s Chronic Arthritis Association – http://www.ccaa.org.uk
The CCAA is run by both parents and professionals and is open to all who are concerned with the welfare of children with juvenile idiopathic arthritis (JIA).

Directgov – http://www.direct.gov.uk
This is a government public service website. The Disabled people section has many links to information, including several about employment support, house adaptation support, financial help and disabled rights.

DLF – Disabled Living Foundation – http://www.dlf.org.uk
This is a national charity that provides impartial advice and information about equipment/assistive technology designed to enable older and disabled people to live more independently.

The National Rheumatoid Arthritis Society is a UK patient-led charity exclusively dedicated to supporting the approximated 677,000 people in Britain with RA, as well as their families, carers and the healthcare professionals who treat them.

Strongbones Children’s Charitable Trust – http://www.strongbones.org.uk
The charity’s objectives are to help alleviate the pain and suffering of children with bone cancer, arthritis and all other conditions of the bone. It provides financial assistance for medical equipment, holidays, debts and social activities.

Patient.co.uk – http://www.patient.co.uk/health/Rheumatoid-Arthritis/resources
This website contains good signposting for support groups and health articles. It also has patient forums and links to many other relevant websites.
Support for pharmacists and pharmacy technicians

Arthritis and Musculoskeletal Alliance (ARMA) – http://www.arma.uk.net
This is an umbrella association that brings together support groups, professional bodies and research organisations in the field of arthritis and other musculoskeletal conditions.

Arthritis Research UK – http://www.arthritisresearchuk.org
This is a leading charity in the fight against arthritis. It funds research, provides information and regularly campaigns.

The British Society for Rheumatology (BSR) and British Health Professionals in Rheumatology (BHPR) – http://www.rheumatology.org.uk
These are sister organisations for health professionals. BSR is mainly for rheumatologists, while BHPR covers all the allied health professionals who support those with musculoskeletal conditions. They are a useful source of guidelines for the management of RA.

Checklist for planning

To meet the learning objectives you will need to carry out the activities listed in the table below. We’ve given you this list now so that you can start to plan your learning. Although it will only take you about two hours to work through Book 1, feedback from other users suggests that it is useful to plan your activities over a timescale that suits you – perhaps over several days. Try to set yourself a realistic deadline for each task.

<table>
<thead>
<tr>
<th>You will need to:</th>
<th>This will take about:</th>
<th>I will do this by: (Insert date)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Answer the Moving into focus questions</td>
<td>5 minutes</td>
<td></td>
</tr>
<tr>
<td>List three learning needs</td>
<td>5 minutes</td>
<td></td>
</tr>
<tr>
<td>Read the whole booklet</td>
<td>60 minutes</td>
<td></td>
</tr>
<tr>
<td>Undertake the practice points</td>
<td>20 minutes</td>
<td></td>
</tr>
<tr>
<td>Make notes for the talking points</td>
<td>10 minutes</td>
<td></td>
</tr>
<tr>
<td>Work through your own Directing change scenario</td>
<td>20 minutes</td>
<td></td>
</tr>
</tbody>
</table>
Moving into focus

Consider the following questions. Use them to focus your thoughts and stimulate your learning. Are you confident you know the answers?

1. What signs and symptoms would you expect to see in a patient newly diagnosed with RA?

2. At what point in the management of RA does the National Institute for Health and Clinical Excellence (NICE) recommend the use of disease-modifying antirheumatic drugs (DMARDs)?

3. What would a disease activity score 28 (DAS28) of 3.0 tell you about the current level of disease activity in a patient with RA?

4. What key pieces of lifestyle advice would be of benefit to people with RA?

5. One of your patients has just been diagnosed with RA. Where would you signpost them to for advice and support on health and social issues?
What do you want to learn?

Write down three things that you would like to gain from this *focal point* learning unit. These will help you plan your own CPD entry. You will need to tell others about them at the *focal point* event.

1. 

2. 

3. 

Now you have completed your reflection and planning for this *focal point* unit, it’s time to undertake the background reading.
Reading

1. Rheumatoid arthritis

1.1 What is rheumatoid arthritis?
Rheumatoid arthritis (RA) is a chronic, progressive and disabling autoimmune disease that is characterised by pain and inflammation of synovial joints. If left untreated, this inflammation leads to destruction of joints, which is responsible for the deformity and lack of mobility seen in patients. It is a systemic disease, which causes fatigue as well as affecting the heart and lungs.

1.2 The impact of RA
RA is the most common form of inflammatory arthritis, affecting 580,000 adults in England, which is approximately one percent of the population. 1 It can start at any age but has a peak onset between 35 and 50 years of age. As with some other autoimmune diseases, it affects three times as many women as men.

The disease has a huge effect on society, both directly with the costs of medical care and indirectly through the potential loss of financial and social independence of patients. A 2010 report by National Rheumatoid Arthritis Society (NRAS) found that the overall cost to the UK economy of productivity losses due to RA is almost £8 billion per year, while the NHS expenditure on RA is around £700 million. 2

RA also has a huge impact on the lives of the individual, with pain and fatigue affecting their quality of life and ability to work. Work-related disability is particularly common in RA as three-quarters of people diagnosed are of working age. 1 NRAS conducted a survey of people with RA in 2007 and reported that almost 29.3 percent gave up work as a result of their condition – of these, 28.4 percent do so within one year of diagnosis, and well over half do so within six years. 3

The pattern and progression of RA varies between individuals so it is impossible to predict the impact on any one person’s life but early diagnosis and treatment can prevent joint destruction, disability and systemic effects, enabling patients to continue to live an active life.

1.3 Pathogenesis
In early RA the synovium becomes inflamed (see Figure 1, below); there is an effusion into the joint space and this causes joint swelling, leading to pain and stiffness. Once triggered, synovitis becomes self-sustaining. This sustained inflammation of the synovium also leads to the formation of pannus, which is a
granulation tissue (similar to scar tissue). Pannus grows across and erodes the cartilage; the resultant inflammatory onslaught deforms and erodes the bone surface. Long-standing inflammation and effusion distend the joint capsule causing the ligaments to become lax. The combined effects of joint damage, muscle wasting, instability and continued use lead ultimately to joint deformity.

After a variable period of time, synovial inflammation may subside either spontaneously or because of treatment. If little structural damage has occurred the joint may appear clinically or radiologically normal. If the joint has been damaged during the period of active inflammation then deformities will persist and may worsen as secondary degenerative changes follow.

**Figure 1: Joint degeneration in RA**

![Joint degeneration in RA](Image)

### 1.4 Causes of RA

The exact cause of RA is unknown but it seems to be multifactorial. There is a genetic component, as illustrated through twin studies, but other factors are involved too. The fact that the disease affects three times as many women as men indicates a hormonal component while other risk factors include smoking and obesity. The roles of other environmental factors such as infection, diet, caffeine and alcohol consumption have also been studied but there is little conclusive evidence to suggest they have an impact on the development of RA.
2. Presentation, diagnosis and monitoring of RA

2.1 Symptoms

*Figure 2: Hands showing visible signs of RA*

The classic presenting symptoms and signs of RA are joint related and include:

- pain, which is generally worse after rest
- stiffness of variable duration but especially in the morning and usually lasting over 30 minutes
- swelling and loss of function of joints
- warm, hot joints that are tender to the touch.

Any synovial joint may be involved. However, the most commonly affected joints are: the wrists; the proximal interphalangeal (PIP) and the metacarpophalangeal (MCP) joints of the hands (the distal interphalangeal joints are spared); the knees; ankles and the small joints of the feet. RA is mostly a symmetrical disease, which is an important sign when considering a diagnosis (see Figure 3).

*Figure 3: Joints of the hand*
RA is a systemic disease and there may also be extra-articular symptoms, including:

- rheumatoid nodules
- effects on eyes, lungs and heart
- fatigue
- anaemia
- weight loss.

The course of the disease is variable in different patients. For example, approximately ten percent of patients develop an acute and rapidly progressive disease that results in disabling joint deformities. A further 20 percent experience a sudden onset of symptoms followed by a prolonged clinical remission. The remainder initially experience mild, intermittent symptoms, which gradually resolve over a period of weeks or months and then recur, often with greater severity.

2.2 Diagnosis

Evidence now shows that rapid intervention at the early stages of the disease can prevent joint destruction, so early diagnosis is essential. Patients presenting with symptoms in primary care should be referred as soon as possible to a rheumatologist for diagnosis.

NICE\(^6\) suggests that patients with persistent synovitis should be referred if an examination shows:

- a history of ever having experienced prolonged morning stiffness
- both swelling and tenderness in affected joints, particularly small joints
- involvement of PIP and MCP joints
- symmetrical joints are affected
- an inability to make a fist or flex fingers
- a positive MCP squeeze test (ie, pain when pressure is applied to MCP joints two to five, similar to a handshake).
Diagnosis of RA is based on signs and symptoms, supported by biochemical and radiological investigation. There is no one definitive test for RA and the following may be used to make a diagnosis.

- Rheumatoid factor (RF) – around 75 to 80 percent of people with RA test positive for RF. However, it is not always present in the early stages of RA so a negative result should not be used to rule out RA. The test also produces a false positive result in 20 percent of people without RA, so results should be considered alongside clinical signs and symptoms.

- Anti-cyclic citrullinated peptide antibody (Anti-CCP) – this new test is more specific in detecting RA than the RF test and is helpful when there is a negative test for RF or to inform decision making before starting DMARDs.

- C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) – these tests are used to monitor disease activity; raised levels of these two indicate inflammation but they are not specific to RA and may not always be raised in small joint disease.

- Full blood count (FBC) – because 80 percent of people presenting with RA are anaemic.

- X-ray, ultrasound and MRI – these may be used to check for joint damage.

- Urea and electrolytes, liver function and lung function – these are often tested too, as baseline measurements are needed before starting many RA therapies.

### Practice point 1

Spend a few minutes watching the following NRAS video on the importance of early diagnosis in RA: [http://www.nras.org.uk/about_rheumatoid_arthritis/nras_dvd_for_early_diagnosis.aspx](http://www.nras.org.uk/about_rheumatoid_arthritis/nras_dvd_for_early_diagnosis.aspx)

Listen to Jean’s account and make a note of the symptoms she experienced, and then think about the questions you could ask someone if you suspected they may have symptoms of RA.
2.3 Comorbidities

The long-term prognosis for RA patients is dependent not only on the successful management of joint disease but on how well any coexisting conditions are managed. The most common include:

- cardiovascular disease: the incidence of ischemic heart disease and heart failure is higher than those without RA, most likely due to atherosclerosis resulting from inflammation

- cancer: the second most common cause of mortality in RA patients, in particular – lymphoma, skin cancer and lung cancer. Increased levels of smoking in RA patients may contribute to the level of lung cancer

- infections: RA patients are at increased risk of infection, particularly pulmonary infections. This is compounded by the use of immunosuppressants such as DMARDs, biologicals and corticosteroids

- osteoporosis: RA increases the risk of developing osteoporosis and this risk is further increased by the use of corticosteroids

- depression: pain, loss of mobility and, in many cases, unemployment, are contributory factors to developing depression. NICE CG79 recommends that a psychologist should form part of the multidisciplinary team.

2.4 Monitoring

Patients with newly diagnosed RA should be monitored on a monthly basis until the disease is controlled to an agreed level. This includes measurement of CRP and their disease activity score 28 (DAS28).

DAS28

The DAS28 is a score between one and ten that reflects how active the RA is. It is calculated using an equation based on three components:

- Checking for swelling and tenderness of 28 joints (hands, shoulders, elbows, wrists and back – but not feet)
- ESR or CRP
general wellbeing, as judged by the patient on a visual analogue scale of one to ten.

**Table 1: Disease activity levels in RA as indicated by DAS28 score**

<table>
<thead>
<tr>
<th>DAS28 score</th>
<th>Disease activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;5.1</td>
<td>High</td>
</tr>
<tr>
<td>&lt;5.1 and &gt;3.2</td>
<td>Moderate</td>
</tr>
<tr>
<td>&lt;3.2 and &gt;2.6</td>
<td>Low</td>
</tr>
<tr>
<td>&lt;2.6</td>
<td>Patient in remission</td>
</tr>
</tbody>
</table>

For more information on DAS28, have a look at the NRAS video: *Know your DAS score for health professionals*, which is available from:
http://www.nras.org.uk/about_rheumatoid_arthritis/established_disease/disease_activity_score_das/das_video_downloads.aspx

The society also produces a DAS28 *Quick reference guide* that you might find useful to share with patients, which can be found here:

Once a patient’s RA is controlled, they can expect an annual check-up for comorbidities and complications as well as any more frequent tests they may need to monitor potential adverse drug reactions (ADRs).

### 3. Management of RA

The goals of RA management are to:

- relieve pain and inflammation
- prevent joint destruction, with the aim of disease remission
- preserve or improve functional mobility
- maintain a patient’s normal lifestyle.

This is achieved through a combination of drug therapy and lifestyle changes, including rest, exercise, education, emotional support, occupational therapy and physiotherapy, ideally co-ordinated through a named healthcare provider who is responsible for their care. Patients are encouraged to take responsibility for managing their condition and there is a wide range of support to enable them to do this effectively.
In this section we will look at the current medical approaches to the management of RA:

- symptomatic pain relief
- disease modification
- treatment of flares
- use of biologicals
- surgery.

In section 4 we will consider lifestyle changes and the role of the pharmacy team in supporting patients with RA.

3.1 Symptomatic pain relief

3.1.1 Analgesics

Simple analgesics such as paracetamol, codeine or dihydrocodeine and combination preparations can be useful for pain relief. As they have no anti-inflammatory effect their use in RA is limited, but some patients may find them of benefit, especially if taken regularly. They may also decrease the need for non-steroidal anti-inflammatory drugs (NSAIDs).

3.1.2 NSAIDs

Non-selective NSAIDs are the drugs of choice for symptomatic pain relief in RA because when taken regularly at full dose they have both an analgesic and anti-inflammatory action. The choice of NSAID for a particular patient is based on a number of factors (including relative efficacy, toxicity, concomitant drugs, concurrent disease states, the patient’s age and renal function) but ibuprofen at a dose of 1.6 g to 2.4 g daily would be first choice for most, due to its low side-effect profile. Where NSAIDs are used long-term, a proton pump inhibitor (PPI) should be co-prescribed to minimise gastrointestinal damage.8

Patients should have some pain relief from the first dose, and full analgesia within a week. The anti-inflammatory effect should be achieved within three weeks. If this is not the case, then an alternative NSAID can be considered but bear in mind that ten percent of all patients will not respond to any NSAID.
As RA patients are at increased risk of cardiovascular (CV) complications, the risks of taking NSAIDs should be discussed with them before treatment starts. The class effect of NSAIDs increasing the risk of CV complications is currently under debate but the general consensus is that naproxen has the lowest risk at therapeutic levels, making it a good choice of NSAID in RA.\textsuperscript{9,10}

The selective cyclo-oxygenase-2 inhibitors, etoricoxib and celecoxib lie at the higher end of the CV risk spectrum so they should not be used routinely in RA. A balance must be struck between symptom relief versus CV and gastrointestinal (GI) risk.\textsuperscript{11}

3.2 Disease-modifying antirheumatic drugs (DMARDs)

DMARDs have been available for many years but it is only recently that the importance of early and aggressive use to prevent disease progression has been understood.

Newly diagnosed patients with active RA should start on a combination of DMARDs within three months of the onset of persistent symptoms. This should consist of methotrexate and at least one other DMARD. If this is not clinically appropriate then methotrexate or another DMARD should be given as monotherapy, with a rapidly escalating dose. Once the disease is under control, drugs can be stepped down to lower levels that still maintain disease control.\textsuperscript{8}

The concept of using combination therapy is not unlike that used in the control of blood pressure and aims to improve disease control without resulting in adverse effects from excessive doses of individual agents. Using lower doses of different drugs reduces the incidence of type-A reactions (ie, those that are predictable and dose-related). It is also possible that the combination of different modes of action produces an additive, perhaps synergistic, effect.

DMARDs have a slow onset of action, with benefit not being seen until after two to three months. Consequently, counselling is very important to ensure that patients do not give up taking their medicines as a result of not feeling that they are gaining any benefit from them. In the interim, the use of NSAIDs or corticosteroids may be necessary.

It may take four to six months of treatment for a full response. If one of these drugs does not show objective benefits after six months, it should be discontinued. Unfortunately, studies suggest that within two years of starting a DMARD, 50 percent of the patients will have stopped taking the drug because of a lack of efficacy or a problem with adverse effects. Since there are a limited number of DMARDs that most rheumatologists would consider to have any effect, it is clear that a patient who may be more susceptible to adverse effects or tolerance could get through this list of drugs fairly quickly.
Choice of DMARD
NICE recommends that methotrexate is used first-line, along with at least one other DMARD (unless the patient is pregnant or has other relevant conditions). Any combination can be used, ensuring a balance between maximising therapeutic effect and minimising toxicity. It is important to be aware that the severity of RA varies between patients – and within the same patient over time – and that individuals may have unrelated concomitant medical problems that can affect agent selection.

3.2.1 Immunosuppressants

Methotrexate
Methotrexate has a relatively short onset of action (about one month). It is the first-line treatment for RA, with or without one or more DMARDs. Dosing escalation can be rapid, with a starting dose of 7.5 mg orally once a week, increasing by 2.5 mg weekly to a maximum of 15 to 25 mg weekly.

Both oral and subcutaneous methotrexate are used in RA, with the latter being less likely to cause GI side-effects. Patients may choose to self-inject at home, in which case they often receive their supplies direct from a homecare company, bypassing the community pharmacy. It is vital that the pharmacist is aware of this to ensure they are able to monitor interactions and ADRs effectively.

Folic acid use in RA
Folic acid decreases the incidence of side-effects such as stomatitis, nausea and diarrhoea. It is prescribed (unlicensed) with methotrexate at a dose ranging from 5 mg weekly to 5 mg daily, but is omitted on the day the methotrexate is taken because it can affect absorption of methotrexate.

Before starting on methotrexate, patients should have baseline measurements taken to enable monitoring of hepatic and pulmonary ADRs. The risk of hepatic toxicity is increased with increased alcohol intake. Patients should be advised to keep their intake to a minimum and well within national limits during methotrexate therapy.
Pulmonary complications in the form of pneumonitis (inflammation of the lung) are rare but are potentially lethal. The classic presentation is rapid dyspnoea (shortness of breath), which may result in death after a few days. Any patients on methotrexate mentioning shortness of breath or coughing should be advised to stop their methotrexate and to seek immediate medical attention.

Methotrexate is also teratogenic so reliable contraception must be used during therapy, and conception avoided for at least six months after stopping the drug. Finally, while there is a clinically significant interaction between NSAIDs and methotrexate, leading to an increase in the toxicity of methotrexate, it is usually necessary (and an acceptable risk) to continue using NSAIDs in patients with RA. You need to ensure that the patient is receiving close monitoring when methotrexate or NSAIDs are initiated, or when the dosage of methotrexate is increased.\(^\text{13}\)

In 2006 the National Patient Safety Agency (NPSA) published an alert due to the number of deaths of people taking methotrexate. It recommended that those taking oral methotrexate should carry a methotrexate monitoring booklet and the pharmacist should ask to see this every time they dispense a prescription.\(^\text{14}\) If you are not familiar with the NPSA alert, the information is on the agency’s website: [http://www.nrls.npsa.nhs.uk/resources/?entryid45=59800&q=0%c2%acmethotrexate%c2%ac](http://www.nrls.npsa.nhs.uk/resources/?entryid45=59800&q=0%c2%acmethotrexate%c2%ac)

**Leflunomide**

Leflunomide has both anti-inflammatory and immunomodulatory properties, and is used in moderate to severe RA. It has a rapid onset of action (four weeks) and improvement may continue for four to six months. Its long half-life means it can be given as a loading dose of 100 mg a day for three days and then reduced to a maintenance dose of 10 to 20 mg a day. However, many prescribers do not routinely use the loading dose as it may be associated with severe nausea and diarrhoea in the initial stages, so 10 to 20 mg is the usual starting dose. The most common side-effects are GI disturbances, reversible alopecia, rash and hypertension. The active metabolite remains in the body for a long period, so in the case of a severe ADR, a swap to another DMARD, or if conception is planned, a washout procedure with colestyramine or activated charcoal must be carried out.

**Azathioprine**

The immunosuppressant azathioprine is used at a dose of 1.5 to 2.5 mg/kg daily in divided doses for RA. Side-effects are common and 10 to 20 percent of people cannot tolerate it. It is withdrawn if there is no response within three months.

**Ciclosporin**

Ciclosporin is used in patients with severe disease who have failed on other treatments or who are unsuitable for other DMARDs. It is particularly valuable
when used together with methotrexate in patients with very active early disease. It appears to have an efficacy comparable with other DMARDs but it is not as well tolerated due to hypertension and nephrotoxicity. The usual starting dose is 2.5 mg/kg a day, increased gradually after six weeks to a maximum of 4 mg/kg a day according to tolerance and response. A full clinical response is not expected until 12 weeks after starting therapy.

3.2.2 Other DMARDs

**Gold (sodium aurothiomalate)**
Gold may be given by intramuscular (IM) injection. Following a test dose of 10 mg, it is given at a dose of 50 mg weekly until there is remission (usually once 300 to 500 mg has been given). Toxicity with gold is a problem so monitoring is carried out before each injection. It affects a wide range of systems including the skin, kidney, blood, lungs and liver. Despite the toxicity, gold is still a useful option in patients who cannot tolerate sulfasalazine, leflunomide or methotrexate.

**Sulfasalazine**
Sulfasalazine appears to be comparable with parenteral gold in efficacy but it is much better tolerated so is more commonly used. It is administered as enteric-coated tablets at an initial dose of 500 mg a day, increased by 500 mg at weekly intervals to a maintenance dose of between 2 to 3 g a day in divided doses.

The most serious side-effects include haematological abnormalities but they are relatively rare; they usually occur during the first three to six months and are reversible on cessation of treatment. Sulfasalazine has the characteristic of colouring body fluids orange, including urine and tears, so may stain soft contact lenses.

**Penicillamine**
Penicillamine is prescribed orally for severe RA at a usual maintenance dose of 500 to 750 mg daily, then gradually reduced in remission. It can cause loss of taste at around six weeks but this generally returns after another six weeks. It is rarely used these days, as its efficacy is poor.
Antimalarials (hydroxychloroquine and chloroquine)
Antimalarials are less effective than other DMARDs but are generally well tolerated and blood tests are not mandatory. They have a slow onset of action, taking up to six months to have an effect. Hydroxychloroquine is used to treat moderate RA, usually at 200 mg twice daily, in combination with other DMARDs. Chloroquine is used less frequently as it is more toxic than hydroxychloroquine. Doses should be calculated using ideal body weight to prevent excessive dosing in obese patients. The main side-effect of the antimalarials is ocular toxicity so patients should have an eye test at least annually.

Practice point 2
Clearly summarise the key counselling points for DMARDs in patient-friendly words. When you have done this, have a look at the Arthritis Care leaflet *Drugs and complementary therapies* to see how your list compares to theirs. You can find it by typing the title into the search engine on the charity’s website: http://www.arthritiscare.org.uk

3.3 Treatment of flares
Corticosteroids
During a flare, patients generally get an increase in pain and swelling of the joints, coupled with fatigue and fever. Immediate treatment is required to reduce long-term joint damage and corticosteroids produce rapid relief from these inflammatory symptoms. Corticosteroids can be given orally but are usually given IM for treatment of several joints, or intra-articularly into specific joints.

Corticosteroids may have a role in disease modification, but they are not recommended for long-term use due to their side-effects. They should only be used long-term when all other options, including biologicals, have been tried. Once commenced, it is often difficult to withdraw corticosteroids as the disease may flare when the dosage is reduced.
Local corticosteroid injections

Intra-articular steroids such as dexamethasone, hydrocortisone, prednisolone, methylprednisolone and triamcinolone acetonide provide effective symptomatic relief by reducing the inflammation in patients who have one, or only a few, affected joints. Patients should rest the limb for 24 hours after injection. They will usually notice a benefit within 48 hours, which may persist for several months.

The frequency with which joint injections may be repeated remains controversial. They may be given at intervals of three to five weeks or more, depending on the control of ongoing symptoms and flares. If there is a very frequent need for injections, this may indicate that DMARDs are not controlling the condition well enough, and that treatment should be modified.

Where multiple joints are affected, methylprednisolone and triamcinolone are used for IM injection.

For very severe disease, especially with extra-articular manifestations, pulses of 1 g of intravenous (IV) methylprednisolone are sometimes given as a short infusion (over 30 to 60 minutes) every other day for three days. This pulse therapy may be safer than long-term oral steroids as the overall dosage is lower and the frequency of injections can be controlled.

Systemic corticosteroids

Prednisolone 7.5 mg daily may have a role in moderate to severe RA of less than two years' duration however after two to four years the dose should be tapered off to reduce long-term side-effects. It should only be used long-term if the risks have been explained and all other treatment options have been offered.

Talking point A

Which side-effects of long-term corticosteroids are of particular significance for patients with RA and how can these be minimised? Consider lifestyle changes and drug therapy.
3.4 Cytokine modulators (‘biologicals’)

The use of biological DMARDs is an important advancement in the management of RA. They are expensive and not without risk but in most cases the benefits outweigh the risks, allowing many people with RA to carry on with their work and social lives in a way that wasn’t possible previously. Biologicals are only prescribed by specialists, usually in secondary care, so community pharmacists do not see the prescriptions and may not even be aware that patients are taking them, which could have implications for how they support patients to manage their RA.

A number of biological agents are now recommended for use in RA, including tumour necrosis factor inhibitors (see Table 2 below) as well as abatacept, rituximab and tocilizumab. Anakinra is licensed for RA but not recommended by NICE.8,11

The major risk of biological therapy is the increased risk of infection, particularly tuberculosis (TB). Before commencing therapy, patients should have a chest X-ray to ensure there is no latent or active infection. Pharmacists should be aware that a persistent dry cough or dyspnoea in a patient taking biologicals could be a sign of TB and patients should be referred urgently to their GP or specialist. Treatment with biologicals should be stopped when patients have severe infections so pharmacists should be vigilant for prescriptions for antibiotics for these patients.

Tumour necrosis factor inhibitors (anti-TNFs)

Five anti-TNF agents are recommended for use by NICE in patients who have had a DAS28 score greater than 5.1 on two separate occasions, one month apart, and have had trials of at least two DMARDs, including methotrexate (unless contraindicated), for six months each.8

Table 2: Dosing regimens for anti-TNF agents used in RA

<table>
<thead>
<tr>
<th>Anti-TNF</th>
<th>Route and frequency of delivery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adalimumab</td>
<td>Self-injected every two weeks, subcutaneously</td>
</tr>
<tr>
<td>Etanercept</td>
<td>Self-injected once or twice weekly, subcutaneously</td>
</tr>
<tr>
<td>Certolizumab pegol</td>
<td>Self-injected every two weeks, subcutaneously</td>
</tr>
<tr>
<td>Golilumab</td>
<td>Self-injected monthly, subcutaneously</td>
</tr>
<tr>
<td>Infliximab</td>
<td>IV infusion, every eight weeks, day admission</td>
</tr>
</tbody>
</table>

Patients who are self-injecting will often receive their supplies directly via a homecare company on behalf of the hospital, bypassing the community pharmacy.
Abatacept
Abatacept prevents the full activation of T lymphocytes. It is licensed for use for moderate to severe RA in combination with methotrexate, for patients who are unresponsive to other DMARDs (including methotrexate or an anti-TNF). It is given as an IV infusion over 30 minutes, repeated at two weeks, then every four weeks thereafter.

Rituximab
Rituximab depletes B lymphocyte production. NICE recommends that it can be used for severe RA that is unresponsive to one or more anti-TNFs. It is given in hospital as a 1 g IV infusion, repeated with a further infusion after two weeks. It must be used in combination with methotrexate and can be repeated at 6 to 12 months if required.

Tocilizumab
Tocilizumab is an interleukin-6 receptor antagonist, used in combination with methotrexate, for patients for whom anti-TNFs and rituximab have failed. It is also licensed for use as monotherapy for those who cannot tolerate methotrexate. It is given by IV infusion, over one hour, every four weeks.

British Society for Rheumatology Biologics Register (BSRBR)
The BSRBR tracks the progress of patients with severe RA and other rheumatic conditions who are taking anti-TNF therapy. Established in 2001, the BSRBR is the largest prospective register of rheumatology patients receiving anti-TNF therapy in the world, with over 19,000 patients currently registered. Details can be found online at: http://www.medicine.manchester.ac.uk/musculoskeletal/research/arc/clinical_epidemiology/pharmacoeconomics/bsrbr/

For more information on the biologicals, see the following NICE technology appraisals:

- NICE technology appraisal 130: *Adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis*
- NICE technology appraisal 186: *Certolizumab pegol for the treatment of rheumatoid arthritis*
NICE technology appraisal 195: Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after failure of a TNF inhibitor

NICE technology appraisal 198: Tocilizumab for the treatment of rheumatoid arthritis

NICE technology appraisal 225: Golimumab for the treatment of rheumatoid arthritis after the failure of previous disease-modifying antirheumatic drugs.

Each of the above technology appraisals is available on the NICE website:
http://www.nice.org.uk

There is further information on biologicals in the CPPE 2 open learning programme Musculoskeletal disorders – advancing your practice, in Booklet 4, Complications and complexities in rheumatology. This programme is available from:
http://www.cppe.ac.uk

3.5 Surgery

Joint surgery is an option when patients are unresponsive to drug therapy. It will not be suitable for everyone but should decrease pain and increase function. Surgery should be considered before damage to the joints is irreversible and may include joint replacement, joint fusion and tendon reconstruction.

4. Lifestyle changes and the role of the pharmacy team

In this section we consider the role the pharmacy team can play to support and educate patients with RA and look at when we need to refer to other members of the multidisciplinary team. A 2010 report by NRAS, The Year of RA, One Year On, showed that only three percent of services for RA patients have regular input from a pharmacist, so there is plenty of opportunity for service development.16

The Arthritis and Musculoskeletal Alliance’s (ARMA) Standards of Care cover access to support, information and knowledge. They state that pharmacists should make information available on how to recognise the signs and symptoms of RA, managing pain and when and where to seek professional advice. They also outline the need for advice on lifestyle measures to help reduce the risk of developing inflammatory arthritis, including smoking cessation and weight management.5

4.1 The multidisciplinary team

According to NICE CG79,8 people with RA should have ongoing access to a multidisciplinary team to provide the opportunity for periodic assessments of the effect of the disease on their lives and help to manage the condition. Those who wish to know more about their disease and its management should be offered the opportunity to take part in existing educational activities, including self-management programmes.
4.2 Lifestyle advice

Smoking cessation
Smokers have an increased risk of developing RA and the prognosis for those who continue to smoke is worse than for non-smokers. This information, coupled with the fact that RA patients are already at increased risk of CV complications, means that smoking cessation support is a top priority. If you have further learning needs in this area, e-learning is available via the CPPE website: http://www.cppe.ac.uk/e-learning

Weight management
Obesity is a risk factor for RA, so overweight patients should be encouraged to reduce their weight. The pharmacy team can provide support for this through weight management services they may offer, or by signposting to other local services.

For more information and further learning on this topic, there are CPPE open learning programmes available on nutrition and weight management. Both can be downloaded via the CPPE website: http://www.cppe.ac.uk
Exercise
The disabling nature of RA may prevent patients from participating in some sports, but low-impact sports such as swimming, cycling and walking should be encouraged to aid mobility and independence. Exercise improves muscle strength, weight loss and sleep, while decreasing pain and stress. For maximum benefit, a mix of aerobic, strengthening and a range of movement exercises should be included in exercise routines.

Rest
People with RA must balance any exercise with rest. There will be times when rest is needed both to decrease inflammation in joints and to counteract the overwhelming fatigue suffered, especially at times of acute flare.

Joint care
It is essential that RA patients minimise the stress on their joints so self-help devices and support aids, such as shoe horns, jar openers and tap turning devices, are a part of everyday life. Some pharmacies carry stock of these while others may order them in.

Patients with RA may also require medicines-related support, and non-click-lock lids are essential for most. Although the use of a multi-compartment aid (MCA) or monitored dosage system (MDS) might seem to be a practical solution if dexterity is poor, many patients find that they are not necessarily easier to handle than normal bottles. If, however, the use of an MCA or MDS is required, patients will need to be assessed under the Disability Discrimination Act (DDA) 1995. For more information, see the Pharmaceutical Services Negotiating Committee (PSNC) website:

For some people, occasional splinting of joints is beneficial and their occupational therapist will be able to help them with this.

Talking point B
Take a look at the support aids stocked or available to order in your pharmacy, and then think about all the tasks you carry out on a daily basis, from getting up to going to bed.

Now make a list of all the living aids or support you would need if you had active RA. Are you meeting the needs of your RA patients with what is currently offered at your pharmacy?
Diet

There is no strong evidence for benefits of a particular diet in RA but a Mediterranean diet, high in healthy oils, fish and vegetables should be encouraged. As RA patients are at increased risk of osteoporosis, foods high in calcium and vitamin D, such as dairy and green leafy vegetables should also feature. Iron is also important as fatigue and anaemia are features of RA.

There is some evidence of the benefits of long-term omega-3 fish oils to ease joint pain and stiffness. A supplement may provide some benefit for those whose diet does not include high levels of fish oils, but it should be emphasised that these oils will not have any effect on the progression of RA.

4.3 Complementary therapies

There is a wide range of complementary therapies that may provide some relief, including massage, acupuncture, the Alexander technique and reflexology. There is no evidence that they can modify the progression of the disease so patients must be aware that anything they try is to be used alongside their prescribed medication.

The Arthritis Care leaflet Drugs and complementary therapies covers the full spectrum of therapies, and is available here: http://www.arthritiscare.org.uk

4.4 Self-management

Patients should be encouraged to take responsibility for managing their condition as those that do seem to cope much better with the disease. Education programmes can provide information on the drugs used in RA, the benefits of exercise, relaxation techniques and how to communicate with healthcare professionals. Forums on websites such as Arthritis Care and NRAS are also a great source of information and support that you can signpost patients to.
4.5 Over-the-counter (OTC) sales

Many people will delay seeking medical help for the symptoms of RA, so it is likely that they may well purchase OTC pain relief in the form of tablets or gels. The pharmacy team has a role to play here both to identify people who may need referring on for diagnosis and also to ensure that patients being treated for RA are not buying medicines such as ibuprofen when they are prescribed methotrexate, without the knowledge of their GP and specialist team.

Practice point 4

Pharmacists and the wider pharmacy team should be aware of red flag symptoms that may be indicative of an ADR, requiring possible cessation of drug treatment, rather than treatment with OTC medicines.

Listed below are the main DMARDs used in the management of RA. Are you able to identify which of the following symptoms would be a cause for concern for patients taking medicines for RA? Tick all those that apply.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Reason to stop taking drug and seek further advice</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Breathlessness</td>
</tr>
<tr>
<td>Methotrexate</td>
<td></td>
</tr>
<tr>
<td>Sulfasalazine</td>
<td></td>
</tr>
<tr>
<td>Leflunomide</td>
<td></td>
</tr>
<tr>
<td>Ciclosporin</td>
<td></td>
</tr>
<tr>
<td>Antimalarials</td>
<td></td>
</tr>
<tr>
<td>Gold</td>
<td></td>
</tr>
<tr>
<td>Azathioprine</td>
<td></td>
</tr>
<tr>
<td>Penicillamine</td>
<td></td>
</tr>
<tr>
<td>Biologicals</td>
<td></td>
</tr>
</tbody>
</table>
Summary

RA is a chronic, progressive disease characterised by inflammation and pain of joints but it also has a number of systemic effects including fatigue. Unless treated effectively it can leave people immobile and unable to work.

Treatment aims to get patients symptom free but this is not always achievable, as while there is a wide range of drugs available to both delay the progression of the disease and to manage pain, many have high risks of side-effects and toxicity.

The pharmacy team has a role to play in supporting RA patients to optimise their medicines, implement lifestyle changes and know when to seek further help, and to signpost them to the wide range of support groups and resources available.
Directing change

Here we offer you three scenarios that you can use to inform the way you plan to change your practice.

These consider:

- **skill mix – the right person for the task.** This scenario is about encouraging pharmacists and pharmacy technicians to work together and share responsibilities.
- **medicines use reviews (MURs).** This scenario is about achieving the maximum benefit for patients and pharmacists.
- **advanced practice.** This scenario is about preparing for the profession’s future roles or your own future specialty.

Read through the scenarios and choose the one that you would like to discuss further with colleagues at the focal point event. Write down how you would respond to the situation, structuring your response around the following themes:

- the resources you expect to use
- the training required
- the evidence supporting your decision
- the government or national guidelines supporting you
- any local initiatives relevant to the scenario.

### Skill mix – the right person for the task

At lunch you overhear one of your staff asking a colleague if she saw how swollen Mrs Edwards’ hands were when she came in to buy a tube of diclofenac gel today. What steps could you take to ensure that your full team are able to identify and support patients with RA?
Medicines use reviews (MURs)

Patients on NSAIDs are included in the high-risk medicines national target group for targeted MURs. What would you need to include in a checklist for RA patients when completing a targeted MUR?

Advanced practice

As a pharmacist with special interest (PwSI), a prescriber or a consultant pharmacist, what services could you develop to improve the care you offer to patients with RA?
# Checklist for action

At this point in the learning programme you will have carried out the following.

<table>
<thead>
<tr>
<th>I completed this on:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>I have answered the Moving into focus questions</td>
</tr>
<tr>
<td>I have listed three learning needs</td>
</tr>
<tr>
<td>I have read the whole book</td>
</tr>
<tr>
<td>I have undertaken the practice points</td>
</tr>
<tr>
<td>I have made notes for the talking points ready to share at the event</td>
</tr>
<tr>
<td>I have worked through my own Directing change scenario</td>
</tr>
</tbody>
</table>

Signed: _____________________________________________________________

Date: ___________________________________________________________________

Take this booklet with you to your focal point event. Make sure that you know when and where it is and what time it starts. Enjoy your learning.
References

All weblinks in the references list below were accessed in August 2011.


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Email: info@cppe.ac.uk
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Fax: 0161 778 4030
Website: http://www.cppe.ac.uk

Address:
Centre for Pharmacy Postgraduate Education
School of Pharmacy and Pharmaceutical Sciences
1st Floor, Stopford Building
The University of Manchester
Oxford Road
Manchester M13 9PT

Do you have any comments on your focal point learning experience? Email: feedback@cppe.ac.uk

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