A FIFTY-TWO-YEAR-OLD woman is referred to the early arthritis outpatient clinic by her GP. The GP's letter states she has a four-week history of pain in her finger and lower limb joints. The patient reports "walking like a disabled person" and that she has never had this problem before. Blood tests (performed by the GP) show a raised ESR (erythrocyte sedimentation rate). Her previous medical history includes hypertension, uterine fibroids and iron-deficiency anaemia. Her medication consists of:

- Amlodipine 5mg od
- Ferrous fumarate 210mg tds
- Diclofenac 50mg tds
- Co-codamol 8/500 qds prn

The medical registrar takes a brief medical history and carries out an examination, which reveals synovitis in the wrists, metacarpophalangeal (MCP) joints and proximal interphalangeal (PIP) joints of both hands, and synovitis in both ankles. The patient complains of early-morning stiffness that persists for up to two hours. Her hands and wrists have been tender and swollen for two months. Swelling and pain in both knee joints and her feet have made walking difficult.

The registrar performs a number of blood tests, including a full blood count (FBC), liver function tests (LFTs), urea and electrolytes (U&Es), inflammatory markers and antibodies associated with autoimmune inflammatory joint diseases. He also performs an infection screen to rule this out as a cause.

The patient's disease activity score 28 (DAS28) is calculated and she is sent for X-rays of her hands, feet and chest. This shows early erosive change at the fifth metatarsal head but no other abnormalities.

A provisional diagnosis of rheumatoid arthritis (RA) is made and the patient is asked to

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**Rheumatoid arthritis: a patient’s journey (I)**

This case study aims to help you understand the diagnosis of rheumatoid arthritis, the different medicines that may be prescribed and the support you can give patients.

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**Panel 1: Classification criteria for RA**

The scoring system consists of four categories. A score of at least 6 out of 10 is required for diagnosis.

<table>
<thead>
<tr>
<th>Joint involvement</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</td>
<td>2</td>
</tr>
<tr>
<td>4–10 small joints</td>
<td>3</td>
</tr>
<tr>
<td>&gt;10 joints (at least one small joint)</td>
<td>5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Serology (at least one positive result is needed for classification)</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative RF and negative ACPA</td>
<td>0</td>
</tr>
<tr>
<td>Low-positive RA or low-positive ACPA</td>
<td>2</td>
</tr>
<tr>
<td>High-positive RA or high-positive ACPA</td>
<td>3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Acute phase reactants (at least one abnormal result needed)</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>

<table>
<thead>
<tr>
<th>Symptom duration</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ six weeks</td>
<td>0</td>
</tr>
<tr>
<td>≥ six weeks</td>
<td>1</td>
</tr>
</tbody>
</table>

Key: RF = rheumatoid factor; ACPA = anti-citrullinated protein antibodies; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate.

*Adapted from the American College of Rheumatology and EULAR classification criteria for rheumatoid arthritis.
What common symptoms are associated with RA? RA is a chronic autoimmune condition. It presents as a polyarthritis, sometimes developing acutely over a few days or, more commonly, over weeks to months. Fatigue and diffuse muscle-skeletal pain may occur before there is visible swelling of the joints. The disease commonly presents with swelling, tenderness and stiffness in joints, usually those of the hands, wrists, knees, ankles and feet. Morning stiffness is a common early feature. “Boggy” synovial tissue may be felt on examination. However, RA is not purely a disease of the joints and extra-articular manifestations can affect the lungs, skin, blood, eyes and other organs. The European League Against Rheumatism (EULAR) uses a score-based algorithm in diagnosing RA (see Panel 1).

What is the role of corticosteroids in managing RA? Corticosteroids are often used as a bridging therapy to reduce symptoms and disease activity when waiting for the therapeutic onset of a DMARD or when changing from one DMARD to another. Owing to the long-term side effects associated with corticosteroids it is not ideal to use them for long but in resistant cases it may be necessary to include them because the disease cannot be controlled with standard biologic and DMARD therapy alone. Depending on the number of affected joints, corticosteroids may be injected directly into the joint (intra-articular), or given as an IM depot injection or as short- or long-term oral therapy, tapered as rapidly as clinically feasible. They produce rapid relief of inflammatory symptoms and may have a role in disease modification, but their use, at high dose in particular, is restricted because of their long-term side effects, such as osteoporosis, peptic ulceration, diabetes mellitus and hypertension. Low-dose oral prednisolone may be used intermittently if the disease cannot be controlled by other means. For severe disease, particularly where there are extra-articular manifestations, pulsed IV infusions of methylprednisolone may be given, although with the introduction of newer therapies this is now less common. Patients with repeated exposure to corticosteroids are at high risk of glucocorticoid-induced osteoporosis. The fall in bone mineral density associated with corticosteroids is highest within the first few months. Consideration should be given to the need for bone protection with a bisphosphonate and calcium plus vitamin D supplementation.

The prescription
The patient takes her prescription to the hospital pharmacy. She asks the pharmacist if she should take the new medicines in addition to her usual painkillers. What are the important differences between the non-steroidal anti-inflammatory drugs (NSAIDs)? The differences in anti-inflammatory effects of the various NSAIDs are small, but there is wide variation in the incidence of side effects and patients differ in their response. If a patient does not respond to one NSAID he or she might respond to another. However, it is important to give a chosen NSAID an adequate therapeutic trial before switching. Pain-relieving benefits begin after the first dose, but maximum analgesia takes up to a week to develop and anti-inflammatory action up to three weeks.

Gastrointestinal bleeding and perforation occur in around 1% of patients and result in significant morbidity and mortality. Piroxicam, ketoprofen, indomethacin, naproxen and diclofenac are all associated with an intermediate risk of gastrointestinal side effects; azapropazone is associated with the highest risk and ibuprofen the lowest. The cyclo-oxygenase-2 (COX-2) selective agents etoricoxib and celecoxib are as effective as traditional NSAIDs but have a lower incidence of gastric side effects. The options for reducing gastric side effects due to NSAIDs are to avoid them and use simple analgesia; to use an NSAID with the fewest associated gastrointestinal side effects and at the lowest possible dose; to prescribe a gastroprotective agent (proton pump inhibitors are probably best); or to prescribe a selective COX-2 inhibitor. All NSAIDs, including the COX-2 inhibitors, however, are contraindicated in the presence of active peptic ulcer disease. Concomitant aspirin therapy greatly increases the gastrointestinal risks of NSAIDs and severely reduces any gastrointestinal safety advantages of COX-2 selective agents.

Panel 2: DAS28 and its significance
DAS28 is a disease activity score based on a 28-joint count. It is calculated from the number of tender and swollen joints, the patient’s ESR or CRP and a self-determined patient assessment of general health status according to a 100mm visual analogue scale. A score of more than 5.1 indicates high disease activity; 3.2 and up to 5.1 indicates moderate disease activity; between 3.2 and 2.6 indicates low disease activity; and <2.6 indicates remission.

DAS28 is often used to determine when treatment with a biologic should be started, and to evaluate the patient’s response. An adequate response is defined as an improvement in the DAS28 of 1.2 points or more. A drawback associated with using DAS28 as an indicator for changing therapy is that some patients may not have particularly high inflammatory markers, but still have severe disease.

DAS28 may also be raised by the perception and reporting of pain by patients and the presence of pre-existing long-term damage. Variations in the score will be caused by different individuals making the assessment, and any sensory, communication or learning difficulties a patient may have.

Panel 3: Methotrexate is first choice
Methotrexate is highly effective in the management of RA, both as a monotherapy and on the basis of its ability to increase the efficacy of biologic medicines (see Part II, to be published next week). No other DMARD has shown superiority in terms of clinical efficacy and meta-analyses have confirmed tumour necrosis factor inhibitor (TNFi) monotherapy (also called anti-TNF) is not superior to methotrexate in improving signs and symptoms of RA.

Methotrexate is generally used as a first-line agent (unless comorbidity precludes its use). It has an onset of action of about a month, and can be given orally or by subcutaneous or IM injection. It tends to be given by injection when patients are unable to tolerate oral doses because of gastric side effects, or where doses of 25mg or more are being given. The starting dose tends to be 7.5–10mg once a week, then gradually adjusted according to response and tolerance. Patients should be clearly counselled that methotrexate should only be taken once a week.

Common side effects include mouth ulcers (stomatitis) and nausea. Folic acid is commonly prescribed to counteract these, at 5mg once daily, although other regimens are used. Most will omit the dose on the day of methotrexate therapy to avoid any potential impact on the latter’s efficacy.

The use of methotrexate has been associated with haematological, hepatic and pulmonary toxicity. Because of the drug’s potential to suppress bone marrow and cause liver toxicity it is essential that certain blood tests are performed regularly. All patients should have baseline FBC, U&E and LFTs and these should then be performed regularly throughout treatment.

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Recent epidemiological studies lend support to the view that some increased cardiovascular risk may apply to all NSAIDs irrespective of their baseline risk, and not only to chronic users. The greatest concern relates to chronic users of high doses, especially of the COX-2-selective agents and diclofenac. Diclofenac should no longer be prescribed in patients with established ischaemic heart disease, peripheral arterial disease, cerebrovascular disease or congestive heart failure (NYHA II–IV). Evidence suggests that naproxen is associated with a lower thrombotic risk than both the COX-2 selective agents and diclofenac. Patients should use the lowest effective dose and the shortest duration of treatment necessary to control their symptoms. For ibuprofen the risk is low for doses below 1,200mg per day, but doses of 1.6–2.4g daily are needed in RA.

All NSAIDs are contraindicated in severe heart failure and should be used with caution in patients with renal impairment. It also should be noted that although NSAIDs may inhibit the egress of neutrophils (see later), leading to toxicity, this usually remains a theoretical concern. NSAIDs are often prescribed with methotrexate but patients are carefully monitored.

How might new pain relief change the current prescription?
In view of this patient’s history of hypertension it is appropriate to switch to an NSAID associated with a lower thrombotic risk, such as naproxen.

The combination of tramadol with co-codamol 8/500 is inappropriate and needs to be discussed with the prescriber, as does the need for gastric protection.

Paracetamol, used in combination with a weak opiate such as dihydrocodeine, can provide simple pain relief. Although they have no anti-inflammatory properties and will not affect the disease process, such simple analgesics combinations do have a place in both early and late stages of RA.

The World Health Organization’s analgesic ladder is a good starting point for any decision on analgesia. Note that codeine in doses of 8mg, as in co-codamol 8/500, has not been shown to confer any additional benefit over standard paracetamol. The patient may benefit from a prescription of paracetamol 1g qds combined with a separate weak opioid such as dihydrocodeine 30mg qds. It is important to avoid the co-prescription of two weak opioids, for example, tramadol and co-codamol, because this is unlikely to provide additional analgesia and will predispose the patient to unwanted side effects. A laxative, to prevent opiate-induced constipation, may be needed.

Day 14
On Day 14 the patient returns to clinic to be reviewed by a rheumatology nurse specialist. The results from her blood tests are as follows:

- Haemoglobin 11.1g/dl (11.5–16.0)
- Red blood cells 4.85×1012/L (3.80–5.80)
- Platelets 418×109/L (150–400)
- Mean corpuscular volume 78fl (68–82)
- Leucocytes 8.37×109/L (4.00–11.0)
- Neutrophils 2.22×109/L (2.00–7.50)
- Platelet count 418×109/L (150–400)
- Mean platelet volume 10.3fl (5.0–11.0)
- Plateletcrit 0.39 (0.35–0.43)
- Plasma viscosity 1.60 (1.50–1.72)
- Platelets 57×109/L (150–400)
- Mean corpuscular haemoglobin 67pg (64–79)
- Mean corpuscular haemoglobin concentration 0.36 (0.34–0.37)
- Neutrophils <0.5 (0.5–1.0)
- Lymphocytes 0.38×109/L (0.6–1.0)
- Lymphocyte proliferation 55% (40–60)
- Blood urea nitrogen 5.70mmol/L (3.60–7.20)
- Creatinine 77μmol/L (50–110)
- Calcium 2.47mmol/L (2.20–2.60)
- Phosphate 1.47mmol/L (0.80–1.50)
- Alanine transaminase 12IU/L (0–40)
- Aspartate aminotransferase 25IU/L (0–40)
- Gamma glutamyl transpeptidase 12IU/L (0–40)
- Albumin 35g/L (36–48)
- Bilirubin total 17μmol/L (0–20)
- Bilirubin indirect 6.4μmol/L (0–10)
- Vertebral height 2cm (2.5–3.0)
- C-reactive protein (CRP) 5.7mg/L (<10.0)
- Rheumatoid factor (RF) 25IU/ml (<20)
- Anti-cyclic citrullinated peptide (anti-CCP) antibody titre >10: positive
- Anti-neutrophil cytoplasmic antibody (ANCA) screen negative

What is DAS28?
The patient still has a number of swollen joints. The DAS28 is calculated and recorded (see Panel 2).

The patient reports that the injection and painkillers she was given reduced some of her pain and stiffness.

A formal diagnosis of seropositive RA is made. The nurse explains what RA is and how it is managed. She gives the patient a prescription for a DMARD and a form to have blood tests (FBG, U&Es, LFTs and inflammatory markers) two weeks later. The patient is asked to return to clinic after four weeks.

Sulfasalazine Sulfasalazine (enteric-coated) is indicated in mild-to-moderate disease. It has an onset of action of six to 12 weeks. In order to reduce nausea the dose is usually titrated up from 500mg qd, increasing at weekly intervals to 1g bd. Haematological abnormalities have occurred with sulfasalazine and, although these are rare, patients should be advised to report unexplained bleeding, bruising, sore throat, fever or malaise. Patients should also be warned that sulfasalazine can colour urine red and stain contact lenses. Baseline FBCs and LFTs should be performed and repeated intermittently throughout treatment.

Leflunomide Leflunomide inhibits the synthesis of pyrimidine nucleotides in response cells (particularly T-cells) and reduces pro-inflammatory cytokines. Studies have shown it to be at least as effective as sulfasalazine and methotrexate, and for quality-of-life measures some evidence suggests superiority. When given as a loading dose of 100mg qd for three days followed by a maintenance dose of 10–20mg daily its therapeutic effect starts after four to six weeks, and further improvement may be seen for up to six months. However, many centres do not use this loading dose regimen because patients are unable to tolerate the gastrointestinal side effects associated with it. Leflunomide use has been associated with both haematological and hepatotoxic side effects. An FBC and LFTs must be performed before therapy is initiated, and then every two weeks for the first six months, followed by every eight weeks. When leflunomide and methotrexate are used in combination extra caution is advised. Leflunomide can also cause hypotension — blood pressure should be checked before starting leflunomide and regularly after — and men and women are required to use adequate contraceptive measures during treatment, and a washout protocol must be followed for any patient considering starting a family.

Gold Although injectable gold (sodium aurothiomalate) has been shown to be efficacious in the management of RA, its use is limited due to its unfavourable side effect profile. Due to the risk of anaphylaxis an initial 10mg test dose should be given in the first week of treatment, followed by a maintenance dose of 50mg the following week. Administration is by deep IM injection. Patients should be monitored for 30 minutes following each dose. FBC and urine (for proteinuria) should be checked after six days, just before giving the next full dose of 50mg IM. The maintenance dose of 50mg every week is given until the first signs of remission occur. At this point the interval between injections should be extended to two weeks until full remission occurs. The interval between injections can then be increased progressively to three weeks, four weeks and then, after 18 months to two years, to six weeks.

Azathioprine Azathioprine is an oral purine analogue that inhibits lymphocyte proliferation. It becomes biologically active after metabolism by the liver to 6-mercaptopurine. Bone marrow suppression and liver toxicity are associated with its use and FBCs and LFTs should be performed during treatment. Renal function should also be monitored because the drug is renally excreted. Azathioprine may also be used for steroid-sparing.

Ciclosporin Ciclosporin works by impairing the function of B- and T-lymphocytes. Dose-related hypertension and nephrotoxicity are common side effects. FBCs should be performed during treatment and liver and renal function monitored. Ciclosporin drug levels are not routinely measured when it is used for the management of RA.

What is the significance of RF and anti-CCP? RF and anti-CCP are antibodies directed against one or more of an individual’s own proteins. These auto-antibodies may be detected in the blood of patients with RA and, along with other tests, are used in diagnosis.
RF is the initial defining autoantibody in RA. It is an antibody against a portion (Fc) of IgG. RF and IgG combine to form complexes that contribute to the disease process. However, a positive result may have another cause and a negative result does not rule out RA. Around 80 per cent of patients with RA will be positive for RF and this may precede symptom onset by several years. The presence of RF is associated with a poorer prognosis. Other conditions associated with an elevated RF include chronic hepatitis, primary biliary cirrhosis, chronic viral infection, bacterial endocarditis, leukaemia, infectious mononucleosis, systemic sclerosis and systemic lupus erythematosus.

Raised anti-citrullinated protein antibodies (ACPA; also known as anti-CCP) has been relatively recently recognised as a marker for RA. Post-translational modification of arginine residues to citrulline is the antigen recognised and it has a higher specificity for distinguishing RA from other rheumatic diseases. The presence of ACPA may also provide predictive symptoms of RA by many years and it is highly predictive of the future development of RA in healthy individuals and patients with undifferentiated arthritis. ACPA-positive RA is associated with increased joint damage and lower remission rates. ACPA-positive and ACPA-negative RA are associated with different genetic and environmental risk factors and are increasingly viewed as two distinct disease entities.

When should a DMARD be started and which are commonly used? All patients with confirmed RA should be started on a single DMARD or whether it is more appropriate to prescribe a combination. Current National Institute for Health and Care Excellence guidance recommends that all patients with newly diagnosed active RA should be offered two DMARDS as first-line treatment, ideally within three months of the onset of persistent symptoms. However, European guidance suggests that DMARD monotherapy may be more appropriate in DMARD-naive patients. Reasons include variations in glucocorticoid use in trials comparing DMARD combination and monotherapy, which resulted in non-comparative treatment arms, plus difficulties in evaluating toxicity and efficacy when two DMARDS are started together. Physicians may, therefore, prefer to start with a single agent with close monitoring and rapid dose escalation, with early addition of a second agent where appropriate.

The precise mechanism of action of DMARDs is unclear. There is good evidence that they inhibit the activity of inflammatory cytokines. Certain cytokines have been shown to play an important role in the pathogenesis of RA. Activated T-cells also play a role in the early induction of RA. Methotrexate and leflunomide have both been shown to inhibit T-cells.

The agent of choice is methotrexate (see Panel 3, p146). This is considered the “anchor” drug in RA, but its use may be contraindicated in some patients or therapy may have to be discontinued due to side effects. Other currently recommended DMARDs include sulfasalazine, leflunomide and injectable gold (see Panel 4). Azathioprine and ciclosporin may be used occasionally for progressive disease refractory to other DMARDs, or where a biologic is occasionally used. The antimalarials hydroxychloroquine and chloroquine may also be of use in milder disease. They show some efficacy as a monotherapy with respect to the signs and symptoms of RA but they have not been shown to inhibit structural damage sufficiently compared with other DMARDs. They may also be combined with other DMARDs in the management of RA, but it is not established if they confer additional efficacy.

Penicillamine is no longer used in the management of RA due to its poor side effect profile and lack of efficacy compared with other agents.

**New prescription**

The patient visits the outpatient pharmacy with a prescription for oral methotrexate 10mg once a week for two weeks, then 15mg once each week for two weeks in conjunction with folic acid 5mg daily, except on the day the methotrexate is taken.

**What counselling would you give with methotrexate?** Although methotrexate is a safe medicine when used appropriately, deaths have occurred as a consequence of patients taking it incorrectly. The patient must understand how and when to take the medicine, plus the need for regular blood monitoring. It must be clear that methotrexate is taken only once a week and all patients prescribed it should be reconsulted every time they are issued with a prescription, irrespective of how long they have been receiving treatment.

Important points to cover when counselling a patient prescribed methotrexate are listed in Panel 5. National Patient Safety Agency guidance recommends that all patients taking methotrexate should be issued with a core patient information leaflet and a hand-held monitoring booklet. The prescriber should provide the patient with information about the benefits and risks of treatment. “As directed” should not be used and patients should be clear on the number of tablets they are taking and on which day of the week. There should also be consistency on the strength of the tablet issued — ideally, patients should be supplied with only the 2.5mg strength to avoid confusion. When dispensing the prescription it should be clearly pointed out which is the methotrexate container and which is the folic acid container, so the patient is able to differentiate between the two.

### Part 2

Find out what happened next — follow this case in part II, to be published on The Pharmaceutical Journal next week. Part II will focus on biologic agents used for RA: when it is appropriate to use them, checks needed, associated risks and switching options.