Diagnosis and management of rheumatoid arthritis

GERALD TRACEY

Early recognition and treatment of rheumatoid arthritis is the key to a more successful outcome. This article discusses the diagnosis of rheumatoid arthritis and its recommended management.

Of the millions of people in the UK suffering from musculoskeletal problems, up to one million have a rheumatic condition, including approximately 690,000 adults with rheumatoid arthritis. Rheumatoid arthritis is the most common autoimmune inflammatory arthritis in adults. Women are two to three times more likely to be diagnosed with rheumatoid arthritis, and around three-quarters of patients were first diagnosed at working age. The cause of rheumatoid arthritis is not known.

Susceptible patient groups:
- Female > male
- Smokers
- Anti-cyclic citrullinated peptide (anti-CCP)/rheumatoid factor (RF) positivity
- Peak age 50–75 years.

NICE recommendations
In recent years, the importance of early recognition of symptoms and diagnosis has emerged. NICE recommends referral of any person with persistent synovitis with an unknown cause to a rheumatologist. Refer urgently (within two weeks), if any of the following applies:
- Small joints of the hands (see Figure 1) or feet are affected; more than one joint is affected.
- There has been a delay of three months or longer between the onset of symptoms and the person seeking medical advice.

A national clinical audit of early inflammatory arthritis (EIA) is being carried out by the British Society of Rheumatology (BSR) over three years. All NHS hospitals in England and Wales that provide specialty rheumatology services have been included. NICE’s rheumatoid arthritis quality standard (QS33) statement 2 says that patients with suspected persistent synovitis should be assessed in a rheumatology service within three weeks of referral.

Early results from the audit suggest that there are frequent delays in referral and rheumatology services are struggling to see patients within three weeks of referral. The findings from year one suggested a large variance between areas and trusts.
in reaching this standard. Only 17% of patients were referred within the three days of first presentation and only 38% of patients were seen within three weeks of referral. There are also many local differences in referral criteria to EIA/rheumatology services.

**Diagnosis**

American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) developed classification criteria in 2010, which can help a physician-made diagnosis. The criteria attribute points based on the number of tender or swollen joints. There has to be at least one joint with clinical synovitis. Laboratory tests are included: RF, anti-CCP antibody and acute phase reactants. However, antibody positivity and elevated acute phase reactants are not essential to make the diagnosis. A total score of more than 6 points is considered definite rheumatoid arthritis. For patients with long-standing disease, they can be classified as having rheumatoid arthritis if they previously fulfilled the diagnostic criteria (see Table 1).⁸

**Management**

Early recognition of symptoms and diagnosis is key to a more successful patient outcome. Early review allows faster initiation of treatment and suppression of inflammation.⁹ Studies have clearly demonstrated that response to DMARD therapy is related to duration of symptoms prior to diagnosis.¹⁰

The diagnosis of rheumatoid arthritis can be made with normal autoantibodies/inflammatory markers. Primary care physicians should not wait for investigation results prior to referral if rheumatoid arthritis is suspected. Early referral to a specialist rheumatology clinic has been associated with better results.⁷ The management of rheumatoid arthritis is summarised in Figure 2.

**Primary care**

When patients present with joint symptoms suggestive of inflammatory arthritis, initial treatment by primary care should focus on analgesia. This can include paracetamol, codeine or compound analgesics. Standard NSAIDs or selective COX-2 inhibitors are also options in primary care. Corticosteroids should only be initiated in secondary care after review.⁶

**Multidisciplinary care**

The management of rheumatoid arthritis involves a multidisciplinary approach through a rheumatology clinic (occupational therapy, physiotherapy, psychology and patient support) along with patient education.

The following professionals may be involved in the care of patients with rheumatoid arthritis as part of the multidisciplinary team:
- Occupational therapist – Help with everyday activities; splints, wrist supports, pacing advice
- Physiotherapist – Specific muscle/joint functioning, eccentric concentric exercise programmes
- GP – Assessment and management of co-morbidities including cardiovascular risk and consideration of bone health
- Podiatrist – Foot care, appropriate footwear
- Rheumatology nurse specialist – Practical advice and support
- Orthopaedic surgeon – Joint replacement surgery

**Joint distribution (0–5)**

<table>
<thead>
<tr>
<th>Joints Category</th>
<th>Score</th>
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<tbody>
<tr>
<td>1 Large joint</td>
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<tr>
<td>2–10 Large joints</td>
<td>2</td>
</tr>
<tr>
<td>1–3 Small joints (large joints not counted)</td>
<td>3</td>
</tr>
<tr>
<td>4–10 Small joints (large joints not counted)</td>
<td>4</td>
</tr>
<tr>
<td>&gt;10 Joints (at least one small joint)</td>
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**Serology 0–3**

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<th>Serology Type</th>
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<tr>
<td>Low positive RF or low positive ACPA</td>
<td>2</td>
</tr>
<tr>
<td>High positive RF or high positive ACPA</td>
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**Symptom duration**

<table>
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<tr>
<td>&gt;6 weeks</td>
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**Acute phase reactants**

<table>
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<th>Serology Type</th>
<th>Score</th>
</tr>
</thead>
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<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>

| RF = rheumatoid factor; ACPA = anti-citrullinated protein (anti-CCP) antibodies; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate |

**Table 1.** American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) 2010 rheumatoid arthritis classification criteria⁸

- Smoking cessation.

**Nonpharmacological management**

Various nonpharmacological approaches to treating rheumatoid arthritis exist, the aim being to complement drug-based therapies. These include the following:
- Exercise
- Sleep
- Diet
- Weight loss
- Management of co-morbidities (eg cardiovascular risk, glycaemic control)
- Smoking cessation.

**Corticosteroids**

Corticosteroids are often used acutely when the diagnosis of rheumatoid arthritis has been made. Systemic steroids are often utilised (oral prednisolone, intramuscular or intravenous methylprednisolone). Intra-articular steroids can be used for particularly swollen or painful joints. Steroids have powerful anti-inflammatory effects by regulating gene transcription and stimulating the synthesis of lipocortin.¹¹ They are usually offered in the short term when patients first present.

The side-effects of corticosteroids are well documented and include, but are not limited to:
• Weight gain
• Impaired glycaemic control
• Gastritis
• Mood disturbances (including mania, depression and psychosis)
• Disruption of circadian rhythm
• Increased appetite.

Long-term effects of corticosteroids include the development of Cushing’s syndrome, diabetes, gastric ulcer, osteoporosis and cataracts/glaucoma. These long-term effects are often related to cumulative dose received and high-dose therapy.

Disease-modifying antirheumatic drugs
The first-line treatment for patients newly diagnosed with rheumatoid arthritis includes a conventional disease-modifying antirheumatic drug (DMARD) or a combination of DMARDs (one of which should be methotrexate) plus corticosteroids. Ideally treatment should be initiated within three months of symptom onset.

Methotrexate
NICE now recommends that patients with newly diagnosed rheumatoid arthritis should be offered a combination of DMARDs (if appropriate), one of which should be methotrexate. If combination therapy is not an option then an emphasis needs to be placed on rapid dose escalation.

Methotrexate is a structural analogue of folic acid that competitively inhibits the binding of dihydrofolate to the enzyme dihydrofolate reductase. Its mechanism of action is likely to involve T cell suppression via its effects on purine and pyrimidine metabolism; however, the mechanism is not fully understood.

Methotrexate is available as an oral or subcutaneous preparation. It is a once-weekly medication. The usual dosage range is 7.5mg–25mg weekly. There is variable oral absorption and it is excreted renally. Methotrexate usage is contraindicated if the patient’s estimated glomerular filtration rate (eGFR) is lower than 30ml/min. Higher oral doses may have decreased bioavailability.

Side-effects of methotrexate include:
• Gastrointestinal effects (eg nausea, loose stools)
• Stomatitis
• Abnormal liver chemistry, typically mild elevations in hepatic transaminases
• Rash, often on extremities
• Central nervous system symptoms (eg headache, fatigue, malaise, reduced concentration)
• Alopecia
• Fever (either directly drug-related or due to infection)
• Haematologic abnormalities, particularly macrocytosis, in addition to infrequent but severe myelosuppression.

Adverse effects of methotrexate include:
• Respiratory effects – methotrexate-associated lung injury, eg pulmonary toxicity, lung fibrosis, pneumonitis
• Liver effects – hepatocellular toxicity, liver fibrosis
• Bone marrow effects – agranulocytosis, bone marrow suppression.

Folic acid is co-prescribed with methotrexate to reduce the side-effects associated with its use. It also prevents myelosuppression. It is thought to reduce circulating homocysteine levels.

Regular laboratory monitoring is needed for methotrexate (frequency may differ by local guidelines). The BSR recommends checking full blood count (FBC), urea and electrolytes, and liver function tests (LFTs) every two weeks until dose and monitoring are stable over the first six weeks; thereafter the frequency is monthly. This is because of the effects of methotrexate on liver and bone marrow. Elevated transaminases and raised mean corpuscular volume (MCV) are frequent abnormalities found on testing. Alcohol intake should be limited in patients taking methotrexate and at the very most should be within the patient’s weekly allowance.

Women of childbearing age need to be counselled on the need for adequate contraception due to the risk of teratogenicity with methotrexate. Chest X-ray at baseline is also generally recommended.

Methotrexate drug interactions include:
• Acitretin – raises concentration of methotrexate; risk of hepatotoxicity.
• Ciclosporin – risk of toxicity.
• Trimethoprim/sulfamethoxazole – risk of severe bone marrow depression and haematological toxicity.

Prescribers should refer to the BNF for a full list of methotrexate interactions.

Hydroxychloroquine
Hydroxychloroquine is generally considered a safe and well-tolerated DMARD, but is rarely used as monotherapy except in very mild disease. It is frequently used in combination with other DMARDs. The main side-effects include nausea, rash...
and headaches. The recommended dosage is 200–400mg daily. Dosing should be based on weight and the Royal College of Ophthalmologists recommends that the dosage does not exceed 6.5mg/kg daily. This is because of the rare but potentially serious complication of retinal toxicity. Early signs may be a paracentral scotoma affecting acuity and sometimes colour vision. Bull’s eye maculopathy may be noted on examination. It is recommended that patients have eye testing (reading test performance of each eye with reading spectacle correction if worn) at baseline and annually while on hydroxychloroquine. 

**Leflunomide**

This DMARD is frequently used when patients are intolerant to methotrexate or if methotrexate is contraindicated. Leflunomide is absorbed via the gastrointestinal tract, and converted to active metabolite teriflunomide. Its mode of action is through inhibition of pyrimidine synthesis. It has a half-life of around 15 days. Elimination is via the gastrointestinal tract and kidneys. Teriflunomide goes through extensive enterohepatic recirculation. Similar to methotrexate, laboratory parameters should be monitored: monthly FBC, and LFT for the first six months and bimonthly after that.

Adverse effects of leflunomide include hypertension. Patients should have their blood pressure assessed and treated, if necessary, prior to initiation of treatment. Concurrent NSAID use may exacerbate this phenomenon. Frequent blood pressure monitoring is often advised. Other adverse effects of leflunomide include nausea, diarrhoea and rash. Hepatotoxicity can also be a serious complication of therapy. Due to its long half-life, in the case of life-threatening complications, a washout with cholestyramine (8g three times daily for 11 days) or activated charcoal should be considered.

**Sulfasalazine**

Sulfasalazine is a prodrug that combines a salicylate and a sulfa antibiotic. Approximately 90% of the drug reaches the gut where it is cleaved to form sulfapyridine and 5-aminosalicylic acid (5-ASA). The mechanism of action is not fully understood. Sulfasalazine can cause GI upset, rash and yellow-orange discoloration of body fluids. It can lower sperm motility in men (which is reversible with drug cessation). It is considered safe in pregnancy; the BSR recommends 5mg folic acid daily for women on sulfasalazine who are trying to conceive.

As monotherapy, there is debate as to whether sulfasalazine can prevent joint erosions. However, there have been numerous trials where it has been used as part of a DMARD combination, which have shown benefit.

It is recommended that patients taking sulfasalazine have fortnightly blood tests for the first three months, monthly for the next three months, three monthly thereafter or as clinically indicated.

**Azathioprine**

Azathioprine is a derivative of thioguanine, a purine-mimic antimetabolite. Its active metabolite is 6-mercaptopurine. It is

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**Table 2. The Disease Activity Score (DAS28) for the assessment of rheumatoid arthritis disease activity**

<table>
<thead>
<tr>
<th>Disease Activity Score (DAS28)</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>&gt;5.1</td>
<td>High disease activity</td>
</tr>
<tr>
<td>3.2–5.1</td>
<td>Moderate disease activity</td>
</tr>
<tr>
<td>2.6–3.2</td>
<td>Low disease activity</td>
</tr>
<tr>
<td>&lt;2.6</td>
<td>Disease remission</td>
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**DAS28 is a composite outcome measure that assesses:**

- A patient global assessment using the Visual Analogue Score (VAS) – from 0 (very good) to 10 (very bad)
- Clinician assessment of 28 joints to count how many joints are tender and/or swollen
- Either an erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) measurement

The results are combined to produce the DAS28 score, which correlates with the extent of disease activity:

- <2.6 = Disease remission
- 2.6–3.2 = Low disease activity
- 3.2–5.1 = Moderate disease activity
- >5.1 = High disease activity

**Combination DMARD therapy**

NICE recommends combination DMARD therapy for newly diagnosed rheumatoid arthritis (with one of the drugs being methotrexate). Where combination DMARDs are not suitable, rapid titration of monotherapy should be considered.

Disease control is generally assessed using the Disease Activity Score (DAS28; see Table 2), which is a composite score that includes clinician-assessed tender and swollen joints, a visual analogue scale (VAS) and measurement of either erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) (both blood markers of inflammation). Treatment is titrated as per the DAS28 score. It is an important assessment tool for monitoring disease activity and should be used to determine whether an increase (including qualification for biological medications) or decrease of treatment is indicated.

**Biological medications**

NICE recommends adalimumab, etanercept, infliximab, certolizumab pegol, golimumb, tocilizumab and abatacept, all in combination with methotrexate, as options for treating rheumatoid arthritis, only if:

- Disease is severe, that is, a disease activity score (DAS28) greater than 5.1 and
- Disease has not responded to intensive therapy with a combination of conventional DMARDs.
Adalimumab, etanercept, certolizumab pegol or tocilizumab can be used as monotherapy for people who cannot take methotrexate because of a contraindication or intolerance, and when the criteria listed above are also met (TA375).

NICE adds that treatment should only be continued if there is a moderate response, measured using EULAR criteria, at six months after starting therapy, and treatment should be withdrawn if a moderate EULAR response is not maintained.

**TNF inhibitors**

*Adalimumab* is a fully humanised immunoglobulin (Ig) G1 monoclonal antibody that inhibits tumour necrosis factor (TNF) alpha. Adalimumab is administered every two weeks by subcutaneous injection.

*Etanercept* is a recombinant fusion protein that consists of the soluble tumour necrosis factor (TNF) receptor (p75) linked to the Fc portion of human IgG1 (TNFR:Fc). Etanercept is administered subcutaneously, at either 50mg once weekly or 25mg biweekly.

*Golimumab* is a human IgG1 kappa monoclonal antibody specific for human TNF alpha that neutralises TNF alpha activity.

*Cetolizumab pegol* is a human anti-TNF alpha antibody Fab fragment that is chemically linked to polyethylene glycol. The medication neutralises membrane-associated and soluble TNF alpha. Cetolizumab pegol is administered every two weeks by subcutaneous injection, and dosing at four-week intervals can be effective in some patients for maintenance therapy.

*Infliximab* is a chimeric monoclonal antibody directed against TNF. Infliximab is administered via intravenous infusion approximately every six weeks once a steady state has been achieved.

**Other biological agents**

*Abatacept* is a T cell activation inhibitor. It is soluble fusion protein comprising cytotoxic T lymphocyte-associated protein 4 (CTLA-4) and the Fc portion of IgG1 (CTLA4-Ig). Abatacept can be administered either by weekly subcutaneous injection or by monthly intravenous infusion following several loading doses.

*Tocilizumab* is a humanised antihuman IL-6 receptor anti-body of the IgG1 subclass. IL-6 is important for CRP production, the medication neutralises membrane-associated and soluble TNF alpha. Tocilizumab is administered every two weeks by subcutaneous injection or by monthly intravenous infusion following several loading doses.

*Tocilizumab* is a human anti-TNF alpha antibody Fab fragment that is chemically linked to polyethylene glycol. The medication neutralises membrane-associated and soluble TNF alpha. Tocilizumab can be given intravenously or as a subcutaneous preparation. It may be used as a monotherapy for patients intolerant of, or with a contraindication to, methotrexate.

*Rituximab* is a B cell-depleting monoclonal anti-CD20 antibody. Rituximab has NICE approval for use in severe active rheumatoid arthritis in patients who have had an inadequate response to, or who are intolerant of, other DMARDS, including at least one TNF inhibitor. Treatment should be given no more frequently than every six months and should be continued only if there is an adequate response to therapy. Patients with seropositivity, ie RF positive and/or anti-CCP positive, are more likely to respond to rituximab. It is given intravenously, as a course of two infusions two weeks apart, no more frequently than every six months.

Patients on TNF inhibitors and other biological therapy are at risk of life-threatening infections. Consequently, infec-

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**Figure 2. Summary of the management of rheumatoid arthritis**

- Clinically suspected inflammatory arthritis
  - GP/primary care
  - Early urgent referral to rheumatology (to be seen <3 weeks)

- Early review and assessment
  - Early inflammatory arthritis clinic (under care of rheumatologist)
  - Investigations: laboratory/radiology
  - Early initiation of treatment once diagnosis made
  - Corticosteroids (oral or intramuscular)
  - DMARDS: methotrexate (consider first line), leflunomide, sulfasalazine, hydroxychloroquine

- Multidisciplinary approach:
  - Rheumatology
  - GP
  - Nurse specialist
  - Physiotherapy
  - Occupational therapy
  - Orthopaedic surgeon
  - Podiatry

- Early and frequent review (every 1–3 months) of disease activity (DAS28) and drug tolerance
  - Target sustained disease remission or low disease activity
  - Corticosteroids if inadequate disease control, titration of medications

- If disease activity is severe (DAS28 >5.1) despite conventional DMARD therapy consider biological therapy
tions should be treated early and aggressively. As patients are immunocompromised, they may not present with infection in a typical fashion.

**Biosimilars**
According to NHS England, a “biosimilar medicine is a biological medicine that is developed to be highly similar and clinically equivalent to an existing biological medicine. A biosimilar contains a version of an active substance of an already approved biological medicine, which is referred to as the ‘reference medicine’ or ‘originator medicine.’” Biosimilar medicines should be of similar quality and effectiveness to the originator drug. However, the advent of biosimilars means that biological medicines should be prescribed and dispensed by brand name.

**Conclusion**
Within rheumatology services, we aim to reduce joint damage and symptoms through aggressive treat-to-target strategies. The number of medications for the treatment of rheumatoid arthritis is rapidly increasing with new targets in the immune system. The advent of biosimilars has increased competition and will likely reduce the costs of biological medication. Patients who delay seeking medical help and who experience delayed referral to rheumatology services remain among the biggest challenges to early and effective treatment.

**References**

**Declaration of interests**
None to declare.

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