Rheumatoid arthritis (RA) is a chronic systemic autoimmune disease that primarily manifests as inflammation of the peripheral joints in a symmetric pattern. Constitutional symptoms, including fatigue, malaise, and morning stiffness, are common. Extra-articular involvement of organs such as the skin, heart, lungs, and eyes can be significant. RA causes joint destruction and thus often leads to considerable disability, morbidity and mortality. Recent innovative therapies have significantly advanced the treatment of RA; however, up to 40% of patients may not respond to current therapeutic options.

RA has no known cause. Although an infectious aetiology has been speculated, no organism has been proven responsible. It is associated with specific autoimmune dysregulation that may precede the onset of clinical disease by many years. RA has a significant genetic component, and the shared epitope of the HLA-DR4/DR1 cluster is found in up to 90% of patients with RA, although it is also present in more than 40% of controls. Synovial cell hyperplasia and endothelial cell activation are early events in the pathologic process that progresses to uncontrolled inflammation and consequent cartilage and bone destruction. Genetic factors and immune system abnormalities contribute to disease propagation.

There are no entirely specific and sensitive diagnostic tests, so a combination of clinical features, blood tests and imaging are often required to make a diagnosis. Recently, the American College of Rheumatology (ACR) and the European League against Rheumatism (EULAR) developed new criteria for the classification of RA. The new RA criteria

Patients are definitively diagnosed with RA if they score six or more points according to the following criteria:

**Joint involvement**

- One medium-large joint (0 points)
- Two to 10 medium-large joints (1 point)
- One to three small joints (2 points)
- Four 10 small joints (3 points)
- More than 10 small joints (5 points)

**Serology**

- Not positive for either rheumatoid factor or anti–citrullinated protein antibody (0 points)
- At least one of the two tests is positive at low titer, defined as more than the upper limit of normal but not higher than three times the upper limit of normal (2 points)
- At least one test is positive at high titer, defined as more than three times the upper limit of normal (3 points)

**Duration of synovitis**

- Less than six weeks (0 points)
- Six weeks or longer (1 point)

**Acute phase reactants**

- Neither C-reactive protein nor erythrocyte sedimentation rate is abnormal (0 points)
- Abnormal CRP or abnormal ESR (1 point)

Patients receive the highest point level they fulfil within each domain. Abnormal amounts of serum RF are demonstrated by any method for which the result has been positive in fewer than 5% of healthy control subjects. Radiographic changes include erosions or unequivocal bony decalcification localised in or most marked adjacent to the involved joints.

Patients with RA also may present with constitutional symptoms, including malaise, fever, fatigue, weight loss, and myalgias. They may report difficulty performing activities of daily living. Most patients with RA have an insidious onset. It may begin with systemic features, such as fever, malaise, arthralgias, and weakness, before the appearance of overt joint inflammation and swelling. A small percentage of patients with RA have an abrupt onset, with the acute development of synovitis and extra-articular manifestations. Spontaneous remission is uncommon, especially after the first three to six months.

**Early detection and referral**

The importance of early diagnosis in RA has been compared to that in diabetes. Late diagnosis of RA greatly increases the risk of erosive joint damage. Current guidance is that patients with suspected RA should be referred to a rheumatologist as soon as possible so that disease-modifying agents can be started early in the condition.

However, studies suggest there is room for improvement in this respect. The window of opportunity in which disease-modifying drugs can prevent joint damage is only a few months. The British Society for Rheumatology standard is for a rheumatologist to see the patient within 12 weeks of onset.

A diagnosis of RA should be suspected and early, urgent referral made when there is: persistent inflammation of more than one joint; involvement of the MCP/MTP joints; onset of symptoms three months or more; early morning stiffness > 30 minutes’ duration; or suspected persistent synovitis of undetermined cause. Refer even if CRP and ESR are normal or rheumatoid factor negative.
Early detection is now possible by laboratory diagnosis. Antibodies called anti-cyclic citrullinated peptides (anti CCP) occur 10 years before the development of clinical disease. They are highly specific and if the test is available to GPs locally it should be performed before referral.9

**Shared care**
The best management for patients will most likely include a rheumatologist and clinical nurse specialist responsible for initial diagnosis and commencement of treatment, liaising closely with the GP for maintenance and monitoring of the patient’s condition. The British Society for Rheumatology has published guidelines for shared care as follows:
1. Ensure patients have the information and knowledge to understand the treatment issues
2. Agree that most patients should receive shared care for RA, unless there are exceptional reasons
3. Write all prescriptions in an accurate, legible form, according to the guidance in the current BNF. Whoever prescribes the medication will be clinically responsible
4. Give the maintenance therapy in accordance with the written instructions on the GP information sheets
5. Keep the patient-held record up-to-date with the results of investigations, especially the blood tests
6. Report any adverse effect to the consultant. The GP will ensure that the patient is monitored for DMARDs and will take the advice of the consultant if there are any amendments to the suggested monitoring schedule
7. The GP will ensure that the patient is given the appropriate appointments for follow-up and monitoring, and that defaulters from follow-up are contacted to arrange alternative appointments
8. It is the GP’s responsibility to decide whether to continue treatment in a patient who does not attend appointments required for follow-up and monitoring.

**Self-management**
Self-management education complements traditional patient education in supporting patients to live the best possible quality of life. Arthritis Ireland provides nationwide access to highly successful self-management programmes. Whereas traditional patient education offers information and technical skills, self-management education teaches problem-solving skills. A central concept in self-management is self-efficacy/confidence to carry out behaviour necessary for better the understanding of arthritis and joint protection. Rheumatoid arthritis cannot be cured but it can be managed through medications and self-care. The following are important self-care tips:
- **Exercise regularly.** Start a regular exercise programme after checking with your doctor or physical therapist. Different types of RA require different exercises
- **Manage your weight.** Being overweight puts extra pressure on the joints. No particular food group has been proven to reduce the pain and inflammation of rheumatoid arthritis
- **Apply heat or cold.** Heat can ease pain by increasing the flow of blood. A hot shower or a hot bath can reduce arthritis pain. Cold treatment can also decrease the sensation of pain. Ice packs may be recommended during flare-ups. Check with your physical therapist or doctor
- **Do not over-exert your joints.** Maintain good posture, lift with both hands, and use large muscles to lift.

**First-line treatments**
New and active RA first-line treatment (ideally within three months of the onset of persistent symptoms) should offer:
- **Combination of DMARDs** – including methotrexate and at least one other DMARD, for example: azathioprine, ciclosporine, d-penicillamine, hydroxychloroquine, leflunomide, mycophenolate mofetil (MMF), sulfasalazine, together with short-term glucocorticoids
- **Early intervention with DMARDs produces better outcomes,** in the short-term at least.10 They require four to six months for a full response.

The primary aim is to establish a tolerable and effective drug regimen for each patient. Sulfasalazine or methotrexate is often used first because they may be better tolerated. If one drug does not lead to objective benefit within three months a different drug is tried. This was confirmed by the CORRONA database study which found that an improvement in functional ability was associated with a change of drug.11 DMARDs are instituted by specialists as soon as diagnosis and severity of the disease have been confirmed.

'Tight control!' is the aim, which means increasing the therapy whenever the disease is not fully suppressed. Several studies have now shown this gives a significant improvement in symptoms and signs.12

Methotrexate is a first line DMARD with advantage of known effectiveness and long-term safety. Sulfasalazine significantly reduces disease activity and joint inflammation and slows radiological progression.

All the DMARDs have potentially serious, albeit uncom-
mon, adverse effects which limit their usefulness. The most important adverse events relate to liver and bone marrow toxicity (MTX, SSZ, leflunomide, azathioprine), renal toxicity (cyclosporine A), pneumonitis (MTX), allergic skin reactions (SSZ), autoimmunity (SSZ), and infections (azathioprine, cyclosporine A). Antimalarials may cause ocular toxicity. Nevertheless, these drugs, when used with appropriate clinical and laboratory control monitoring, are usually well tolerated. Adverse events typically become rarer after the first to three months. Most adverse events are reversible with cessation of the drugs or with reduction of the doses.

Consider short-term glucocorticoids (oral, intramuscular or intra-articular) to improve symptoms rapidly in newly-diagnosed RA (if not receiving glucocorticoids as part of DMARD combination therapy).17

Offer simple analgesics (Paracetamol, codeine or compound analgesics) in RA when pain control is not adequate. Use oral NSAIDs or COX-2 inhibitors at the lowest effective dose and with a proton pump inhibitor (PPI). When prescribing NSAIDs or COX-2 inhibitors be aware of their potential gastrointestinal, liver and cardio-renal toxicity. If NSAIDs or COX-2 inhibitors are not providing satisfactory symptom control, review the disease-modifying or biological drug regimen.

**Recent trends in drug treatment**

Treatment has shifted to earlier and more intense use of disease-modifying agents. The aim of treatment is to improve symptoms and reduce the later complications and disability. RA is an independent risk factor for cardiovascular disease and suppressing disease activity may reduce co-morbidity.2,3 Combinations of different classes of drugs are being investigated for the treatment of early RA. At any stage, the use of simple analgesia should be considered as an adjunct. Drugs to suppress neuropathic pain, such as carbamazepine or amitriptyline, may be beneficial.

**Biological therapies**

These include infliximab, etanercept, adalimumab, Rituximab, abatacept, tocilizumab.13,14 A revolution has occurred in treating RA due to the realisation that the pro-inflammatory cytokine TNF-alpha plays a central role. In the past 10 years, several agents have been developed that block this molecule and TNF inhibitors significantly improve symptoms and reduce disease activity and joint inflammation. The initiation and monitoring of these drugs is very much the province of the specialist. However, it is important for generalists and members of the MDT to be aware of the how they are used and monitoring issues. Infliximab (Remicade) and etanercept (Enbrel) are very effective in reducing the symptoms and signs of RA in patients who fail to respond to DMARDs and both reduce joint swelling, radiological erosions, malaise and fatigue.15

Clinical effectiveness and side-effect profiles are similar for all these drugs. All have rapid onsets of action from days to weeks. A meta-analysis has concluded that this group of drugs are very effective in the treatment of RA, both in treatment-naive and methotrexate resistant patients.16

Patients at risk of infection (those on high-dose steroids or with uncontrolled diabetes), are excluded from treatment. See also individual drug monographs. Side-effects are generally minor and tolerable and monitoring is not required to the degree necessary with DMARDs. Severe adverse events are unusual but have been reported. TNF is a key regulator of immunity and opportunistic infections, such as tuberculosis (TB), have been reported. Reactivation of TB, worsening of demyelinating disease, suppression of bone marrow and a variety of unusual idiosyncratic side effects can occur.

**Diet and complementary therapies**

There is no strong evidence that patients with RA will benefit from changes in diet. A Mediterranean diet should be encouraged (more bread, fruit, vegetables and fish; less meat; and replace butter and cheese with products based on vegetable and plant oils).1 Complementary therapies may provide short-term symptomatic benefit but there is little or no evidence of long-term benefit.

Advise RA patients who wish to try complementary therapies that they should not replace conventional treatment and this should not affect the care offered by any member of the MDT. One study suggested that cod liver oil could be used as a NSAID-sparing agent in RA patients.17

RA is a chronic autoimmune disease primarily associated with symmetric joint inflammation, fatigue and morning stiffness ultimately leading to joint destruction, considerable disability and mortality. Extra-articular organ involvement, skin, heart, lungs, and eyes can be significant. RA pathogenesis has a significant genetic component, although as yet undiscovered environmental triggers, are undoubtedly important.

Recent innovative therapies represent significant advances to the treatment of RA, however up to 40% of patients may not respond to current therapeutic options, so the search for further novel therapies continues.

The concept of remission for RA patients has now moved from the realms of theoretical possibility to the reality. The next challenge is to examine if we can match specific patients to specific treatments as we move into an era of personalised therapy.

**Amer Saeed** is rheumatology registrar and **Douglas Veale** is consultant rheumatologist at St Vincent’s University Hospital, Dublin

References on request