Rheumatoid arthritis

Rheumatoid arthritis (RA) is a disease of unknown cause that leads to widespread inflammation, predominantly manifesting itself in the joints, with pain, swelling and stiffness. Uncontrolled, it is a progressive disease that damages joints and can lead to joint deformity and difficulties with daily functioning.

Dr Frances Rees, **Specialty Registrar in Rheumatology, Royal Derby Hospital**
Dr Chris Deighton, **Consultant Rheumatologist, Royal Derby Hospital**
email frees@doctors.org.uk

Rheumatoid arthritis (RA) is common, affecting approximately 580,000 people in England.[1] It can present at any time during adulthood, but most commonly during the 6th decade of life.

It can be just as aggressive in an elderly population and requires prompt assessment and treatment to prevent pain and disability.[2]

Recent evidence has proven that commencement of treatment within the first three months of symptom onset is more effective at inducing disease remission and can alter long-term disease progression.[3]

Rheumatologists and NICE therefore advocate prompt referral of any patient with early morning stiffness and persistent synovitis.[4] If the squeeze test (where the metacarpophalangeal or metatarsophalangeal joints are compressed across the joint line) is positive, and particularly if several areas are affected, this should merit referral to the specialist team.

Most specialists would rather see patients quickly, with no tests having been requested, or steroids having been commenced to delay or mask diagnosis.

Treatment

The treatment of early RA is optimised to each individual and involves a multi-disciplinary approach.

Analgesia

Analgesia should be commenced promptly and tailored using the WHO analgesic pain ladder.[5] However just giving analgesia or non-steroidal anti-inflammatory drugs (NSAIDs) if they are not contra-indicated (and in the elderly they often are) is an inadequate response, because even if it relieves pain it does not slow down the damaging nature of the disease.

Steroids

Short-term steroids are used as a first-line treatment to control early joint inflammation, alleviating the initial joint pain and swelling and hastening return to independent function. This may be in the form of joint injections if few joints are involved, tablets, or intramuscular depot injections. Steroids are not routinely recommended for long-term use because although there is evidence that they help to slow down the damaging nature of the disease (unlike NSAIDs), the advantages are often outweighed by the disadvantages over time such as predisposition to infection (even in low doses), weight gain, osteoporosis, diabetes, cataracts, glaucoma and occasionally avascular necrosis of the hip.

DMARDs

In order to minimise the dependence on steroids for symptom relief and slowing disease progression, Disease-modifying antirheumatic drugs (DMARDs) should be introduced immediately. Methotrexate is the DMARD of choice because it is as good as the other DMARDs in head to head studies, and has better tolerability and sustained efficacy long-term compared with other DMARDs.[4] It is given once weekly either orally or subcutaneously when tablets cause side effects or when efficacy is limited to increase bioavailability. The dose is titrated according to response. Commonly experienced side effects with methotrexate include nausea, mouth ulcers, and rash. Serious side effects include bone marrow suppression, infection, pneumonitis, pulmonary fibrosis and liver

cirrhosis.[6] As a consequence patients have a baseline chest radiograph and regular blood monitoring of full blood count and liver function. All patients should be educated to enable them to be vigilant for side effects. As the drug is eliminated via the kidneys, dose adjustments are made if the glomerular filtration rate declines to reduce toxicity.

Folic acid is co-prescribed with methotrexate to reduce side effects. Trimethoprim and sulphonomides should not be prescribed with methotrexate due to increased risk of haematological side effects due to synergistic folate antagonism.

It is important in the early stages to have frequent specialist assessment to ensure adequate suppression of inflammation, with NICE guidelines advocating monthly follow up of active RA until the disease is satisfactorily controlled.[4] Patients should also have access to urgent appointments if they are struggling with a disease flare.

Depending on disease severity methotrexate can be used alone or in combination with other DMARDs to improve disease control eg. sulfasalazine and/or hydroxychloroquine (Plaquenil). The NICE guidelines state that early active RA should be treated with combinations of DMARDs, because studies and meta-analyses suggest superiority of combination therapy over monotherapies.[4] Sulfasalazine is a combination of an aminosalicylate and sulfapyridine. It therefore should not be prescribed in patients with sulphonamide or salicylate hypersensitivity. Common side effects are nausea, rash and diarrhoea. Hepatitis and agranulocytosis are uncommon but serious[6] therefore monitoring of blood counts and liver function occurs.

Hydroxychloroquine is an anti-malarial which was found to be effective in RA. It blocks Toll-like receptors to reduce B and T cell proliferation. Common side-effects are nausea, rash, headache and diarrhoea. Retinopathy is an uncommon but serious side effect therefore annual optician review is recommended. Leflunomide (Arava) can replace or be used in combination with other DMARDs. Its side effect profile is similar to that of methotrexate. It has a long half life therefore if toxicity is suspected washout is required.

Once treatment is established and stabilised, patients need at least annual review to ensure their arthritis is well-controlled and to assess and prevent comorbidities.[4] Existing DMARDs may be titrated up or down or changed due to side effects or inadequate control. If a patient has failed two DMARDs and they have severe active disease NICE has ruled that they should have access to biological agents.

Biological drugs

Biological drugs are created in cell lines and act by inhibiting a specific part of the inflammatory pathway eg. tumour necrosis factor or other cytokines, or B or T lymphocytes, all of which drive RA. They are injectable agents which are very effective and have transformed current therapy. However, they are currently very expensive (eg. anti-TNF drugs are £8–10,000 per patient per year) and therefore there are strict guidelines set by NICE as to which patients are eligible for their use. Drugs that are well established and currently in use are the anti-TNF agents adalimumab (Humira), infliximab (Remicade) and etanercept (Enbrel). Etanercept and infliximab were the first to be recommended by NICE in 2002.[7] In 2010 NICE approved two further anti-TNF agents golimumab (Simponi) and certulizumab pegol (Cimzia).[8-9] It is recommended that these drugs are co-prescribed with methotrexate to improve efficacy unless contraindicated. Patients on anti-TNF require six monthly monitoring to ensure that response is maintained to continue on treatment. If response is inadequate, then treatment is withdrawn. Second-line biological therapy is rituximab (Mabthera), a B-lymphocyte depletory agent.[10] This was approved by NICE in 2007 and is a six monthly infusion. Again, an adequate response to treatment must be demonstrated. In 2010 NICE approved the use of third line agents abatacept (Orencia)[10] (which interferes with antigen presentation to T cells) and tocilizumab (RoActemra) (an IL-6 inhibitor).[11] Newer cytokine, cellular and inflammatory pathway inhibitors are being developed.

The main complications with biological therapy are local injection site reactions, rashes and infection. Most infections are of skin and soft tissue. Infections can be severe due to host immunocompromise. As a result prior to commencement all patients are screened for TB and Hepatitis B and C as these can be reactivated. If a patient on anti-TNF presents with fever and signs of infection the drug should be stopped until the infection is clinically eradicated. If the infection is severe the patient should be admitted for intravenous antibiotics. For some chronic deep seated infections such as septic

arthritis or osteomyelitis, anti-TNF injections should be re-introduced once the infection is clear, and only then with caution, because of the ability of causative bacteria to avoid detection and eradication, and flare up again once the drug is re-introduced. Concerns regarding increased rate of malignancy have not been confirmed when compared with conventional DMARD therapy,[12] but there are concerns over increased rates of skin cancers, so that patients and their carers should monitor their skin surfaces for any suspicious lesions. Anti-TNF use is contra-indicated in patients with previous malignancy, unless this was in the distant past and has been cured. Anti-TNF is also contra-indicated in patients with multiple sclerosis and cardiac failure (New York classification 3 or 4). The British Society of Rheumatology biologics register (BSRBR) was set up in 2001 to monitor long-term effects of therapy, and continues with important work in long-term pharmacovigilance.

Risks

In keeping with other patients with chronic inflammatory diseases, patients with RA have an increased risk of cardiovascular morbidity and mortality. Therefore, during annual review traditional cardiovascular risk factors must be addressed, including smoking, hypertension and hypercholesterolaemia. Patients are at risk of osteoporosis whether they have been exposed to corticosteroid use or not. As RA is a chronic illness, mental health must be assessed as depression is a very common concomitant.

In addition to pharmacotherapies, patients with RA require input from other members of the multidisciplinary team. Physiotherapists, occupational therapists, nurse specialists, orthotists, orthopaedic surgeons and podiatrists can all be involved in the care of RA patients to reduce pain, maintain function and independent living. A well informed and educated patient should be at the centre of the multidisciplinary team.

Conclusion

In conclusion, with new approaches to therapy such as early intervention, intensive treatment with conventional drugs, and use of biological drugs where these fail, patients with rheumatoid arthritis can expect to enjoy an active, independent life fully functioning in society, irrespective of their age. For many elderly patients remission from active disease can be achieved, but in others comorbidities will limit the intensity of treatment that can be used, and minimal disease activity may have to be a compromise. As new technologies develop, the cost of biological agents may reduce allowing greater access.

Physicians should be aware of potentially serious complications of treatment, with all ill RA patients on immunosuppressives being septic until proven otherwise. If in doubt over a RA patient admitted on a general medical take, contact your local rheumatologist for advice.

Conflict of interest: none declared

References

1. National Audit Office. (2009) Services for people with rheumatoid arthritis. The stationary office.
2. Pease CT, Bhakta BB, Devlin J, Emery P. Does the age of onset of rheumatoid arthritis influence phenotype?: a prospective study of outcome and prognostic factors. *Rheumatology* 1999; **38**(3): 228–34
3. Hyrich K. Patients with suspected rheumatoid arthritis should be referred early to rheumatology. *BMJ* 2008; **336**: 215
4. NICE Clinical guideline 79. Rheumatoid arthritis:the management of rheumatoid arthritis in adults. National Institute of Health and Clinical Excellence. Feb 2009. http://www.nice.org.uk/CG79
5. World Health Organization (1996) Cancer pain relief, 2nd edn. World Health Organization, Geneva, Switzerland
6. British National Formulary 61, March 2011. www.bnf.org
7. NICE Clinical guideline 36. Rheumatoid arthritis - etanercept and infliximab. National Institute of Health and Clinical Excellence. March 2002. http://guidance.nice.org.uk/TA36
8. NICE Technology appraisal 186. Certolizumab pegol for the treatment of Rheumatoid arthritis -. Feb 2010. http://www.nice.org.uk/TA186
9. NICE Technology appraisal 225. Golimumab for the treatment of rheumatoid arthritis after the failure of previous disease-modifying anti-rheumatic drugs. June 2011. http://www.nice.org.uk/TA225
10. NICE Technology appraisal 195. Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor. June 2011. http://www.nice.org.uk/TA195
11. NICE Technology appraisal 198. Tocilizumab for the treatment of rheumatoid arthritis. August 2010. http://www.nice.org.uk/TA198
12. Symmons DP, Silman AJ. The world of biologics. *Lupus* 2006; **15**(3): 122–26