National Medicines Information Centre

VOLUME 9
NUMBER 1
2003

ST. JAMES'S HOSPITAL • DUBLIN 8
TEL 01-4730589 or 1850-727-727 • FAX 01-4730596
E-Mail: nmic@stjames.ie

Current Pharmacotherapy of Rheumatoid Arthritis

SUMMARY

- **Rheumatoid arthritis (RA) is a chronic autoimmune inflammatory disease characterised by progressive joint damage. It causes significant morbidity and mortality.**
- **Fortunately, over the past 10 years, there has been a significant change in the management of RA resulting in improved outcomes for patients.**
- **Early aggressive therapy with disease-modifying antirheumatic drugs (DMARDs) is now recommended. Combinations of DMARDs are well tolerated, and often provide greater benefit than monotherapy.**
- **Recently licensed DMARDs include, leflunomide and the biological therapies infliximab, etanercept and anakinra.**

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic systemic autoimmune inflammatory disease associated with polyarticular synovial inflammation leading to joint destruction, deformity and disability.[1] It affects up to 1% of the adult population worldwide and is more common in females.[1] It can occur at any age, with increasing incidence up to the seventh decade of life.[2] The aetiology of RA is unclear, but epidemiological studies indicate a genetic predisposition. It is postulated that RA may result from exposure to an, as yet unidentified, antigen that elicits an immune response only in susceptible individuals. This immune response involves infiltration and stimulation of many inflammatory cells that then release cytokines, causing synovial inflammation and subsequent joint damage.[3] Initial presentation can be roughly categorised into those that have a slow onset of disease (75%), those that have intermediate disease activity (20%) and those that have rapidly debilitating illness (5%).[4] There is an increasing number of agents used in the management of RA. These may be broadly divided into (1) those that provide only symptom relief from pain and inflammation, e.g. non-steroidal anti-inflammatory drugs (NSAIDs) or corticosteroids, and (2) those that retard joint destruction and reduce disability, i.e. DMARDs, including the novel biological agents that target specific inflammatory mediators.

Over the last decade, there has been a change in the approach to the therapeutic management of RA. Traditionally, conservative management centred on symptom control for several years, with DMARDs reserved for when the disease was not controlled.[5] It is now known that permanent cartilage and bone destruction occur early in the course of active RA, and once a diagnosis of RA has been confirmed, DMARDs should be commenced promptly (preferably within 12 weeks), in order to delay disease progression and prevent joint damage, consequently also controlling symptoms.[6-11]

NSAIDs

NSAIDs have analgesic and anti-inflammatory effects, but may not affect the disease process of RA.[13] In practical terms:

- Only one NSAID should be used at any time, at the lowest dose compatible with symptom relief. Early intervention with DMARDs in RA should allow NSAIDs to be reduced or possibly stopped.[12]
- No NSAID is consistently more effective than any other, but some patients who do not respond to or cannot tolerate one drug may respond to or tolerate another.[13]
- It is recommended that the NSAID be changed after one week if there has been no response where an analgesic effect is the desired outcome, or after three weeks where an anti-inflammatory effect is desired. Approximately 10% of patients will not find any NSAID beneficial.[5]

The emergence of the cyclo-oxygenase (COX) 2 selective inhibitors in recent years has led to their widespread use in RA patients. The National Institute for Clinical Excellence (NICE) in the UK has issued guidance stating that COX 2 selective inhibitors (celecoxib, rofecoxib and meloxicam) have equivalent efficacy to nonselective NSAIDs, but there is some evidence that they are associated with fewer gastrointestinal (GI) adverse events.[14] The risk of NSAID-induced complications is particularly increased in patients with a previous clinical history of gastroduodenal ulcer, GI bleeding or gastroduodenal perforation, and the use of even a COX 2 inhibitor should, therefore, be carefully considered in this situation.[14] Concurrent use of a gastroprotective agent may decrease the incidence of GI toxicity with older NSAIDs, but there is currently no evidence that this is the case with COX 2 inhibitors.[12] NICE states that COX 2 selective inhibitors are not recommended for routine use in patients with RA. They should be used, in preference to traditional NSAIDs, only in patients with RA who may be at high risk of developing serious GI adverse effects, e.g. (i) patients over 65 years of age, (ii) patients taking medicines known to increase the likelihood of upper GI side effects (e.g. steroids, anticoagulants), (iii) patients with serious co-morbidities such as cardiovascular disease, renal or hepatic impairment, diabetes and hypertension or (iv) patients requiring prolonged treatment with high doses of NSAIDs.[14] In those patients with cardiovascular disease taking low dose aspirin, the benefit of using a COX 2 inhibitor (to decrease GI toxicity) is reduced. Prescribing preferentially over traditional NSAIDs in this setting is therefore not justified.[15] It must be remembered that COX 2 selective inhibitors also cause all the well-recognised NSAID-associated side effects of fluid retention, oedema and hypertension.[15] *Refer to individual NSAID SmPCs for details of side effects, drug interactions etc.*

CORTICOSTEROIDS

Corticosteroids have a potent anti-inflammatory effect, and produce a rapid improvement in the signs and symptoms of RA. However, long-term use of corticosteroids is associated with well-known significant adverse effects. Their exact place in therapy remains controversial. They are often used early in the course of the disease to reduce inflammation while waiting for DMARDs to take effect.[5] They may also be used for short courses during disease flares. Intra-articular corticosteroid administration can often provide symptom relief from an acutely inflamed joint.[13]

DMARDs

Early DMARD therapy in RA is important to maintain function and reduce later disability.[7] DMARDs currently used in clinical practice include methotrexate, sulfasalazine, ciclosporin, penicillamine, azathioprine, gold, cyclophosphamide, leflunomide and antimalarials e.g. hydroxychloroquine. It may, depending on the specific DMARD, take several weeks or months to see therapeutic benefit. Efficacy, tolerability and convenience are major considerations when selecting appropriate DMARD therapy.[9] Penicillamine and gold[12] are seldom initiated nowadays, and cyclophosphamide[12] is mostly reserved for rheumatoid vasculitis.

Methotrexate or sulfasalazine are common first line therapies in early RA, due to their more favourable efficacy/toxicity profiles.[5,7,16]

Methotrexate: Methotrexate is prescribed as a single dose **once weekly**. It is crucial to be vigilant and ensure that this remains once weekly. Errors have all too frequently occurred, when prescriptions are transcribed or dispensed, e.g. as patients transfer between primary and secondary care, or indeed between specialities. Such errors have resulted in fatalities due to severe bone marrow suppression or renal failure.[16,17]
The nausea and stomatitis associated with methotrexate therapy can be managed by the addition of folic acid. The optimal dose of folic acid has yet to be established, but it ranges from 5mg weekly to 5mg daily, with some centres omitting it on the day of methotrexate administration.[5]

Sulfasalazine: Sulfasalazine has a low risk of serious adverse effects, and monitoring requirements are less arduous. To reduce nausea, the dose is titrated from 500mg daily, increasing at weekly intervals up to 1g twice daily.[5]

Leflunomide: Leflunomide is an oral drug that has both anti-inflammatory and immunomodulatory properties. It acts by inhibiting pyrimidine synthesis in cells involved in the immune response, particularly T-lymphocytes. Leflunomide has a rapid onset of action (4 weeks), and is proven to delay radiological progression in terms of joint erosions. It is at least as effective as sulfasalazine or methotrexate, and is indicated where these agents have not been tolerated, or have failed to control disease. [5,12] A loading dose of 100mg daily for 3 days is used to attain a more rapid steady state between 4 and 6 weeks.[18] This is followed by 10 to 20mg daily.[5] Pregnancy, or an intended pregnancy within 2 years and breastfeeding are contraindications to leflunomide therapy. Cholestyramine can be administered, under specialist guidelines, to aid drug elimination e.g. before conception.[16] Severe liver toxicity has been reported in patients taking leflunomide, and hepatic impairment is a contraindication to its use. Alcohol excess should be avoided. Due to its immunomodulatory effects, caution is also required in patients with immunodeficiency or infections.[12] Leflunomide may potentiate the anticoagulant effect of warfarin.[19]

Combination of DMARDs: Despite the ability of DMARDs to reduce disease activity and joint damage, monotherapy may not lead to true remission in some patients and combination therapy is frequently required. The combination of several traditional DMARDs has shown increased efficacy over monotherapy without a significant increase in toxicity.[6,20,21] Methotrexate is the drug most commonly used in combination.[21] Triple therapy with methotrexate, sulfasalazine and hydroxychloroquine is commonly prescribed, and appears to be effective with an acceptable level of adverse effects.[5,6,12,22] A 'step-down' approach, where DMARDs are given as combination therapy from the outset and then tapered down, has shown improvements in disease activity. Sulfasalazine, methotrexate and prednisolone have been used in this way with some success. Another more common approach is to use a 'step-up' regimen, where if monotherapy is ineffective or only leads to a partial response, then a second agent is added.[5] Methotrexate with either ciclosporin[22] or sulfasalazine has been shown to be an effective regimen.[5,6]

DMARD tolerability/monitoring: The value of laboratory tests in patients receiving DMARDs lies in the early recognition of potentially hazardous organ damage, or in the reassurance of the continued safety of the drugs. Table 1 outlines the common monitoring schedules for DMARDs – these have been taken from an amalgamation of published literature sources and are guidelines only; practice may vary between centres. *For full details on DMARD dosage, side effects, monitoring requirements, drug interactions etc., refer to individual SmPCs.*

Table 1: DMARD side effects and monitoring guidelines [5-8,12,16]

Drug	Side effects	Monitoring guidelines	Notes
Methotrexate	Nausea, stomatitis, rash, bone marrow suppression, pneumonitis, liver dysfunction, alopecia	Baseline chest X-ray, pulmonary function, FBC, LFTs, RP. FBC every 1 - 2 weeks until dose stable, then monthly. LFTs fortnightly, then monthly.	Consider monthly RP and urinalysis. Investigate any illness or unexplained cough. Advise to restrict alcohol intake.
Sulfasalazine	GI effects, discolouration of urine/contact lens, nausea, leucopenia, rash, reversible oligospermia, hepatitis, marrow suppression	Baseline FBC, LFTs, RP. FBC every 2 – 4 weeks for the first 3 months, then 3 monthly. LFTs monthly for the first 3 months, then 3 monthly.	Consider 1 – 3 monthly RP and urinalysis.
Penicillamine	Rash, taste disturbance, nausea, myositis, proteinuria, myasthenia, marrow suppression	Baseline FBC, LFTs, urinalysis, RP. FBC and urinalysis every 1 – 2 weeks until dose stable, then monthly	Withhold if proteinuria develops. Consider 6 monthly RP and LFTs.
Azathioprine	Nausea, hepatitis, cholestatic jaundice, marrow suppression, sepsis, lymphoma (late)	Baseline FBC, LFTs, RP. FBC, LFTs weekly for first 4 – 8 weeks, and after dose change, then 1 - 3 monthly.	Can use in patients with renal disease.
Hydroxy-chloroquine	Visual disturbances, retinopathy, rash	Baseline and 6 – 12 monthly assessment of visual acuity	Consider regular FBC.
Ciclosporin	Hirsutism, gingival hyperplasia, hypertension, renal impairment, paraesthesia/tremor/headaches, sepsis	Baseline RP, BP, urinalysis. RP, BP, urinalysis fortnightly for 2 – 3 months, then monthly.	Compare all RP and BP with baseline. If creatinine 30% > baseline, reduce dose. Consider regular FBC, LFTs.
Leflunomide	GI effects, rash, alopecia, hypertension, marrow suppression, liver dysfunction	Baseline FBC, LFTs, RP, BP. FBC, LFTs, BP every 2 - 4 weeks for 6 months, then 2 monthly.	Avoid excess alcohol.
Gold (sodium aurothiomalate)	Rash, stomatitis, marrow suppression, proteinuria	Baseline FBC, LFTs, urinalysis, RP. FBC and urinalysis before each injection.	Withhold if proteinuria develops. Consider 6 monthly RP and LFTs.

FBC = full blood count, LFTs = liver function tests, RP = renal profile (urea, electrolytes and serum creatinine), BP = blood pressure

Biological therapies: Recent advances in the understanding of the pathogenesis of RA, and more specifically, the role of cytokines, e.g. tumour necrosis factor α (TNF-α) and interleukin 1 (IL-1) has led to exciting therapeutic developments. TNF-α and IL-1 cause inflammation, are present in the synovium and lead to recruitment of other inflammatory cells and eventual joint destruction. Both infliximab and etanercept are biological response modifiers that bind and inactivate TNF-α. Infliximab is a chimeric human/mouse anti-TNF monoclonal antibody. Etanercept is a recombinant version of the soluble human TNF receptor. Anakinra is a recombinant human IL-1 receptor antagonist that blocks the activity of IL-1.

Infliximab: Infliximab 3mg/kg is administered intravenously over 2 hours, followed by additional 3mg/kg infusion doses at 2 and 6 weeks after the first infusion, then every 8 weeks thereafter. Methotrexate once weekly must be given concomitantly. Infliximab can cause reactivation of latent TB, hence screening for prior TB, including a baseline chest X-ray is recommended. Common adverse effects include injection site reactions, infusion-related reactions, infections, headache, dizziness, GI effects and abnormal hepatic function. Clinical signs consistent with a lupus-like syndrome have developed rarely. Infliximab is contraindicated in patients with moderate or severe heart failure, tuberculosis or other severe infections.[27]

Etanercept: Etanercept 25mg twice a week is administered subcutaneously. Commonly occurring adverse effects include injection site reactions, fever, infection, headache, rhinitis and dizziness.[24,26] Etanercept has also been associated with serious blood disorders.[16,26] It is contraindicated in patients with active infections.[26] Caution is required in heart failure patients.[26]

Anakinra: Anakinra 100mg is administered subcutaneously once a day. Methotrexate once weekly is given concomitantly. Anakinra should not be used in patients with severe renal impairment. Common adverse effects include injection site reactions, headache, neutropenia and serious infections.[25]

All 3 biological agents – etanercept, infliximab and anakinra have proven efficacy in the treatment of RA. Comparisons of their efficacy across clinical trials is difficult due to differences in study design, study conduct and patient population [28], and currently head to head trials of these agents are lacking.
The long-term immunosuppressive effects of etanercept or of concomitant use of methotrexate with infliximab or anakinra are unknown. There is a concern that continued inhibition of pro-inflammatory markers may increase the risk of infection, other autoimmune diseases, and cancer, particularly lympho-proliferative malignancies.[7,29] Malignancies and CNS demyelinating disorders in RA patients treated with infliximab [23,27] or etanercept [26] have been reported, but a direct causal relationship has not been established. NICE has recommended the use of either etanercept or infliximab for highly active RA in adults who have failed to respond to at least two DMARDs, including methotrexate. Etanercept or infliximab should be withdrawn if severe side effects develop or there is no response after 3 months. Consecutive use of etanercept and infliximab is not recommended.[16,30] The concurrent use of anakinra and etanercept is not recommended due to increased risk of serious infection and neutropenia.[31]

Future developments in the treatment of RA include mycophenolate mofetil, an immunosuppressant currently used in the prophylaxis of transplant rejection; and adalimumab,[4] an anti-TNF monoclonal antibody that is human in origin, and is expected to be tolerated for longer, with potentially fewer allergic reactions.

CONCLUSION

RA is a progressive disease associated with often severe disability, and in some cases premature death. Early diagnosis is important and the rapid introduction of effective early treatment, and the use of combination therapy, has improved the outcome for many RA patients. Furthermore, the development of the newer biological agents that target specific sites of the inflammatory cascade, has dramatically changed the quality of life for RA patients, in particular those with more aggressive rheumatoid disease.

Drug and daily dosage	Cost for 28 days therapy
Diclofenac 50mg tds	€14.24
Celecoxib 100-200mg bd	€29.48 - €58.97
Rofecoxib 25mg od	€34.61
Etoricoxib 90mg od	€37.05
Methotrexate 7.5-20mg weekly (oral)	€1.76 - €4.69
Leflunomide 10-20mg od	€69.69
Infliximab* 3mg/kg (34 –66kg person) Year 1, 8 infusions (€11,046.88) Year 2, 7 infusions (€9,666.02)	 €849.76† €743.54†
Infliximab* 3mg/kg (68 –100kg person) Year 1, 8 infusions (€16,570.32) Year 2, 7 infusions (€14,499.03)	 €1274.64† €1115.31†
Etanercept* 25mg twice a week	€1048.37
Anakinra* 100mg od	€1032.11

*Reimbursable on High Tech Scheme †Calculated from the yearly cost

List of references available on request.