Patient education. FM should be explained as a symptom, such as headache or backache. It is important for patients to be told that they have a real problem which is a biologically based disorder.

Psychological and behavioural management, including cognitive behavioural therapy and relaxation techniques, should be employed at the outset.

Physical therapy improves pain and functional ability and should include strength training, developing flexibility, balance and endurance.

Diet. Important considerations are vitamin D supplementation, emphasis on bone health and reaching an optimum weight.

Pharmacological management. Evidence for the efficacy of different classes of drugs has been categorised as follows:

- Strong evidence – tricyclics (amitriptyline); dual re-uptake inhibitors (SNRI/NSRI – venlafaxine, duloxetine, milnacipran); alpha-2-delta ligands (pregabalin, gabapentin)
- Modest evidence – tramadol; selective serotonin re-uptake inhibitors (SSRIs); dopamine agonists; gamma-hydroxybutyrate
- Weak evidence – growth hormone; 5-hydroxytryptamine; tropisetron, S-adenosyl-L-methionine
- No evidence – opioids; NSAIDs; corticosteroids; benzodiazepine and non-benzodiazepine hypnotics; melatonin; guanifenesin; dehydro-epiandrosterone.

References available at www.cmej.org.za

Use of biological agents in rheumatic disease

ELSA VAN DUUREN, *BMedSci, MB ChB, MSc (Sports Medicine), MMed (Med Phys)*
Rheumatologist, Jacaranda Hospital, Pretoria

Correspondence to: evduuren@mweb.co.za

In a large number of rheumatic diseases the disease process is driven by the immune system. In the past few decades, there have been great advances in our understanding of the immunopathology and pathogenesis of the rheumatic diseases. At the same time, there have been similar advances in the development of drugs, particularly in the field of biopharmaceutical drugs that can target specific components of the immune response central to these diseases. Biological drugs can be monoclonal antibodies or proteins produced by living cells that bind with receptors on various cells to block formation or action of various cytokines or cell mediators, or in other ways change cell function.[1,2]

The area where there has been the most use of these drugs in research and later in the clinical setting has been in the treatment of inflammatory arthritis, particularly rheumatoid arthritis (RA), but also in the treatment of ankylosing spondylitis (AS), undifferentiated spondyloarthritis, reactive arthritis, psoriatic arthritis (PsA) and juvenile idiopathic arthritis (JIA). In these diseases, the biological disease-modifying anti-rheumatic drugs (DMARDs) have made a great difference to patients who have failed conventional synthetic DMARDs, not only in improvement of symptoms and function, but by inhibiting structural damage to joints.[2,3]

The first biological DMARDs to be used in the treatment of inflammatory arthritis were the TNF-alpha blockers. There are now several different TNF-alpha blocking drugs available in South Africa. Infliximab (Revellex) is given as an intravenous infusion every 8 weeks at a dose of 3 mg/kg (5mg/kg for AS), etanercept (Enbrel) is given subcutaneously at a dose of 25 mg twice a week, and adalimumab (Humira) subcutaneously at a dose of 40 mg every second week. All three drugs have been shown to be equally effective in the treatment of inflammatory arthritis and are indicated for these diseases.[3]

The main safety concerns with these drugs, as with any that affect the immune system, have been the potentially increased risk of infection. Clinical trials have shown that the infection risk was comparable to placebo groups on the whole as far as most infections were concerned. The infection of concern, particularly in a high-risk country, is tuberculosis (TB). There is a risk of reactivation of latent TB infection (LTBI) as well as newly acquired infection. TNF-alpha plays a specific role in the formation of granuloma that contains the TB organism in LTBI, and inhibition can lead to breakdown of the granuloma and release of the organisms. All patients are tested for LTBI before starting a biological drug and are treated if the infection is present. The risk of TB has been reduced using this approach, but it is still something to be looked for every time a patient on a biological agent is assessed at follow-up. Other safety concerns are the risk of malignancy and lymphoma, which do not seem to be increased compared with the background population of patients with severe inflammatory arthritis. There have been a few cases of demyelinating disease and patients with any suspicion of such a disease should not receive these drugs. Another contraindication is heart failure, as it can be worsened. Safety in pregnancy has not been established, although specific abnormalities related to the drug have not been seen in babies born to patients on these drugs during pregnancy.[2]

Other biological drugs have become available, namely abatacept (Orencia), rituximab (MabThera) and tocilizumab (Actemra). Abatacept is a selective co-stimulation modulator that inhibits the co-stimulation of T cells important in the RA disease pathogenesis. It is given at a dose of 750 mg or 1 000 mg, depending on the mass of the patient, as an intravenous infusion every month. Rituximab is an anti-CD20 monoclonal antibody which depletes CD-20 positive B cells in the body. The dose for RA is two 1 000 mg intravenous infusions given 14 days apart every 6 months or when a patient again starts to show symptoms of active disease. Abatacept inhibits the cytokine IL-6 and is given with a dosing schedule of 4 or 8 mg/kg every 4 weeks as an intravenous infusion. In clinical trials, the response to all three drugs has been comparable to that seen with the TNF-alpha blockers. The safety of these drugs is similar to that of the TNF-alpha blockers, with the risk of infection remaining the main concern, although the risk of TB seems to be decreased.

The use of biologics in other connective tissue diseases has not been as widely studied. Most are anecdotal studies, as most diseases are uncommon and the clinical picture is variable, making randomised controlled trials difficult. Rituximab has shown promise in treating several connective tissue diseases where conventional therapies have failed, including systemic lupus erythematosus (SLE), various types of vasculitis, Sjögren's syndrome and possibly scleroderma.

The biological drugs have opened new horizons for the treatment of rheumatic diseases and will continue to be important drugs. Unfortunately the technology used to make these drugs is expensive, which

currently severely limits their use, but it is hoped that the price will improve and that we will be able to give the benefit of another type of treatment to a greater number of our patients with rheumatic disease.

Summary

- The biological drugs have made a major impact on the way rheumatic diseases can be treated.
- They have been used mainly in the treatment of inflammatory arthritis.
- Some biologicals show promise in the treatment of other connective tissue diseases, particularly vasculitis and lupus.
- Several of these drugs block cytokines, such as the TNF-alpha blockers and IL-6 blockers, while others block activation of cells that produce cytokines or produce apoptosis in cells (e.g. abatacept and rituximab).
- Currently available drugs are in injectable form used at different time intervals.
- The main concerns in the use of biological drugs have been increased infection rate, particularly activation of tuberculosis.
- On the whole the biologics are relatively safe drugs offering real benefit in previously difficult-to-treat diseases.

References available at www.cmej.org.za

Gout – an overview

B J JANSEN VAN RENSBURG,
MB ChB, MMed (INT), FCP (SA)
Subspecialist in Rheumatology and Clinical Head, Rheumatology, Department of Internal Medicine, Faculty of Health Sciences, University of the Free State, Bloemfontein

Correspondence to: B J Jansen van Rensburg (gninbjvr@ufs.ac.za)

Gout (urate crystal deposition disease) is considered by some to be the most painful and most frequent of all inflammatory joint conditions.[1,2] If not well managed, it may lead to extensive polyarticular joint damage, systemic complications and functional loss.

The initial symptoms are usually acute with joint and soft-tissue inflammation of the foot and first MTP joint in more than 80% of cases. Urate crystals are deposited in multiple peripheral joints and soft tissue as a result of chronic raised uric acid. The disease progresses as the urate pool in the body increases over a period of approximately 10 years from initial asymptomatic hyperuricaemia to a monoarticular attack. Attacks increase in frequency and extensiveness and the disease eventually becomes chronic, tophaceous and polyarticular with systemic complications and nephropathy. Kidney stones in over-producers are common and may provide a clue to the diagnosis of gout. The clinical picture of longstanding gout may mimic rheumatoid arthritis and it is one of the most mismanaged conditions in rheumatology.

The uric acid pool increases with purine intake and internal production related to the breakdown of nucleic acids. Xanthine oxidase is important in the oxidation of hypoxantine to xanthine and uric acid. In the majority of cases the uric acid is raised owing to impaired renal excretion and transport. Dehydration, alcohol and many drugs that depend on renal excretion may influence the serum uric acid levels. A small amount of uric acid is excreted through the gut and has an enterohepatic circulation. Normal serum uric acid levels range from 0.12 to 0.55 mmol/l and normal urate excretion in the kidney ranges from 1.5 to 4.4 mmol/l in 24 hours. It is interesting to note that uric acid acts as a danger signal in the body when tissue is damaged and is a strong inducer of acute inflammation.[3]

Effective management of gout should aim to prevent joint damage and systemic complications. Early intervention and prevention of repetitive attacks improve the outcome. It is possible to decrease the uric acid pool or prevent it from accumulating. With long-term lowering of uric acid the tophi may decrease in size and the volume and kidney function may improve. Two important pillars in the management of gout include lifestyle modification and drug therapy.

Treatment should be tailored according to the individual patient. The following factors should be considered in the management of each patient:[4-7]

- The specific risk factors that relate to gout, including serum urate levels, history of previous attacks and radiographic signs of joint damage.
- The clinical phase of gout.
- General risk factors that predispose the patient to other complications that are commonly noted in the gout patient. Risk factors for cardiovascular and kidney disease include the patient's age, sex, body mass index, fat distribution and related conditions such as hypertension, hypercholesterolaemia, type 2 diabetes and lifestyle factors (smoking, diet and alcohol consumption). It is important to consider drug interactions that may influence urate levels.

The non-pharmacological management of gout is a critical component that is mostly neglected by the practitioner, but may bear the most fruit in the long term. A major goal is reached if the patient understands the basic mechanisms of the disease and feels motivated to comply with treatment and lifestyle adjustments. The patient should be motivated regarding weight loss, diet modifications, fluid intake and alcohol consumption. Adequate water intake prevents dehydration and the precipitation of urate. It is important to note that excessive protein (in any form) may precipitate acute gout – not only red meat. Legumes, nuts and some vegetables are high in protein.[8] Excessive intake of fruit may precipitate acute gout. The basic rule is moderation and a healthy lifestyle.

Drug therapy is limited and the need exists for newer therapies. More drugs are expected to be available in the near future, but may be costly. Prophylactic therapy is indicated when frequent attacks occur and when complications or tophaceous gout are present. Xanthine oxidase inhibitors are effective in over-producers and under-excretors. Allopurinol reduces the production and load of uric acid that needs to be excreted by the kidneys. Gout may worsen when treatment is initiated in patients during an acute attack or precipitated in the patient with high uric acid levels. It is wise to initially give low doses of allopurinol and slowly titrate to higher doses, while covering the patient for acute attacks with low doses of (0.5 - 1 mg) daily colchicine and non-steroidal anti-inflammatory drugs (NSAIDs). The uric acid levels should be monitored monthly and should ideally be lowered to levels below 0.35 mmol/l. It may be necessary to give more than 300 mg of allopurinol daily and in rare cases up to 900 mg daily. Increase by 50 mg to 100 mg monthly according to the serum uric acid and monitor the kidney function and full blood count.

In patients in whom allopurinol toxicity occurs, options include other xanthine oxidase inhibitors (febuxostat), a uricosuric