The early identification of rheumatoid arthritis (RA) is crucial to the success of treating this disease. There is a window of opportunity, thought to be within the first 3 months of diagnosis, in which disease-modifying drugs (DMARDs) should be started to ensure a good functional outcome for the patient.  

This is the most important factor in the treatment of rheumatoid arthritis. DMARD treatment success is well documented in clinical trials and post-marketing research, but erosions of joints still occur in spite of an apparently good clinical response.

Biological treatment can play a role in preventing early bone erosion so its use in early rheumatoid arthritis is becoming more accepted. The use of biological therapies has become established over the last 5 years. More than 400 000 patients have been exposed to biological therapy (approximately 300 patients in South Africa).

As more patients receive biological therapy it is important that practitioners familiarise themselves with these agents. Currently these therapies have been used mainly in resistant cases who have failed standard DMARD therapy. Evidence is emerging that favours the use of these therapies in early RA for optimal disease control and functional benefit.

Etanercept (Enbrel; Wyeth) and infliximab (Revellex; Schering Plough) are registered in South Africa for RA.

**Etanercept**

Etanercept (Enbrel) is a soluble p75 TNF-alpha receptor fusion protein that binds TNF-alpha. It is administered as 25 mg subcutaneously twice weekly or 50 mg once weekly. Studies have shown that it has a rapid onset and when added to methotrexate treatment it is efficacious for patients who have not responded to methotrexate alone. Radiographic damage is significantly less in studies over 2 years comparing etanercept with methotrexate users. All measures of disease activity showed better outcome on etanercept versus methotrexate alone.

**Adverse events** (etanercept is generally well tolerated):

- 37% of patients develop injection site reactions for 3 - 5 days in the first month of treatment.
- Infections: reactivation of latent TB and pulmonary TB is of particular importance in South Africa.
- Opportunistic infections: atypical TB, aspergillosis, cryptococcus, coccidiodomycosis, candidiasis, pneumocystis, histoplasmosis, listeria, nocardia and cytomegalovirus infections can occur.
- Demyelinating disease: confusion, ataxia, dysaesthesia, paraesthesia, optic neuritis, hemiparesis, transverse myelitis have been reported in cases overseas.
- Neoplasia: cases of mostly non-Hodgkin’s lymphoma have been reported, but there seems to be no increased risk other than that seen in RA patients on other therapies.
- Cytopenias are rare, but have been reported.
- Heart failure: cases have been reported, but after adjustment for risk factors, the incidence of heart failure was the same in patients treated with anti-TNF alpha agents and those treated with standard DMARD therapies. None the less, caution is advised in patients with cardiovascular risk.
- Antibody induction: 16% of patients develop antibodies, but they seem to have no effect on efficacy or safety. Forty cases of a lupus-like syndrome were reported in other countries, but patients recovered when the drug was stopped.
- Liver involvement: hepatitis B can be reactivated on etanercept; liver disease with fulminant liver failure has been reported.
- Cases of vasculitis have also been reported.

**Safety monitoring**

- All patients must be tested for latent TB (PPD > 5mm induration) prior to anti-TNF alpha treatment. A recent chest X-ray is mandatory to exclude active TB.
- Live vaccines (i.e. hepatitis, yellow fever, herpes zoster) are contraindicated.
- All infections should be reported and dealt with appropriately. Etanercept treatment should be interrupted during infections.
- All patients must be tested for hepatitis B and C activity, and abnormal liver enzymes prior to the initiation...
of anti-TNF treatment, must be investigated and monitored closely.

- Biological therapy is contraindicated in pregnancy and during breastfeeding.

**Infliximab**

Infliximab (Revellex) is a chimeric human/mouse monoclonal antibody to TNF-alpha. It is administered in a dose of 3 - 5 mg/kg at 2-monthly intervals after a loading period of 6 weeks. Infliximab is usually used in combination with methotrexate for increased efficacy in the long term and the prevention of autoantibodies that can influence the long-term efficacy of the drug.

The benefits of infliximab in active RA were established in the ATTRACT trial, performed in patients with longstanding resistant disease.3 The patients on infliximab and methotrexate had near-complete inhibition of radiographic progression over 3 years.

Studies using infliximab in early disease of less than 3 years’ duration (ASPIRE trial) have shown even more impressive results regarding radiographic progression over 3 years.

Adverse effects are similar to etanercept, with the exception of:

- Infusion reactions varying from mild to severe in 2 - 10% of treated patients. These reactions can occur at any stage of treatment, and are possibly related to the formation of human anti-chimeric antibodies (HACA).

- More cases of latent TB reactivation have been reported worldwide – 97% of cases occur within the first 6 infusions, 15% by the third infusion resulting mostly in extrapulmonary or disseminated TB.

Another TNF-alpha inhibitor, adalimumab, a fully humanised recombinant anti-TNF monoclonal antibody, awaits registration. Many other promising biological therapies are in various stages of research abroad and in South Africa.

Although awaiting registration for psoriatic arthritis, juvenile idiopathic arthritis and ankylosing spondylitis, biological therapies have been proven to be highly effective in the treatment of these diseases.4-5

**Conclusion**

There is a window of opportunity for highly successful treatment of RA in the first year and especially in the 3 months after diagnosis. This is a crucial step in achieving optimal control of disease progression and functional status. The use of optimal treatment in early RA is essential. Patients who do not achieve rapid disease control on standard DMARD therapy should be considered for biological therapy. Studies have shown better radiographic outcome and disease activity control on these agents.

However, it is unfortunately likely that health economic issues will dominate the determination of future optimal therapeutic regimens for early RA, psoriatic arthritis, juvenile idiopathic arthritis and ankylosing spondylitis.

**References available on request.**

**MANAGEMENT OF GOUT**

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The burden of hyperuricaemia (HU) and its related disorders is significant and increasing among black South Africans against a background of a 24.4% prevalence of hypertension, improving socio-economic conditions and changing lifestyle and dietary habits.

HU is defined as a serum uric acid (S-UA) > 0.42 mmol/l in men and > 0.36 mmol/l in women. However, the most important factor is the degree of solubility. As the level rises above 0.42 mmol/l, the tendency for crystallisation and precipitation in joints and soft tissue increases, resulting in clinical disease. Other factors such as acidic pH, decreased temperature, dehydration and trauma also influence solubility adversely.

HU is divided into an asymptomatic phase, acute gouty arthritis, the intercritical period, chronic tophaceous gout and urolithiasis. Comorbid diseases such as hypertension, ischaemic heart disease, obesity, type 2 diabetes mellitus, insulin resistance, hyperlipidaemia and hypothyroidism are important and require appropriate treatment. Uric acid is produced as the breakdown product of purines. HU occurs when there is a primary or secondary problem with either overproduction or underexcretion (Table I).

Management of the HU depends on the clinical phase of the disease.

**Asymptomatic HU**

Only 20% of patients with increased S-UA develop gout or renal stones, therefore not all patients need specific urate-lowering drugs (ULDs). Dietary restriction of purine is impractical and only lowers S-UA marginally (≤0.06 mmol/l). A low caloric diet addressing obesity and insulin resistance seems to be more appropriate. Red meat, some seafoods and alcohol, especially beer and spirits, should be avoided. Dairy products have been shown to be protective and vegetable proteins are not problematical.

If S-UA levels are > 0.72 mmol/l in men and > 0.58 mmol/l in women introduction of ULDs should be considered. Treatment is lifelong, and as

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**Acidosis**

- pyrazinamide/ethambutol

**Dehydration**

**Renal failure**

**Hypertension**

- Drugs (diuretics, low-dose aspirin, pyrazinamide/ethambutol)

**Increased production**

- Haematological malignancies

**Secondary**

- Increased production

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