DRUG THERAPY FOR RHEUMATOID ARTHRITIS

1. **SIMPLE ANALGESIA** (Pain killers)
   - PARACETAMOL (Panadol, Pamol, Paracare)
   - PARACETAMOL & CODEINE (Panadeine, Codalgin, Paracode)
   - DEXTROPROPOXYPHENE AND PARACETAMOL
     (Paradex, now delisted but still a useful analgesia and available under section 29).
   - DIHYDROCODEINE (DHC continus)
   - NEFOPAM (Acupan)
   - TRAMADOL (Tranal, Tramedo)
   - BUPRENORPHINE (Temgesic)

   These medications just relieve pain and may be taken as necessary.

2. **NON-STEROIDAL ANTI-INFLAMMATORY DRUGS** (NSAIDs)
   - ASPIRIN (Disprin, Ecotrin, Aspro-clear, Solprin)
   - IBUPROFEN (Brufen, Nurofen, Panafen, ACT-3, Apo-Ibuprofen, I-Profen, Nuromol or Nurofen Plus (also contains codeine)
   - TENOXICAM (Tilcotil)
   - KETOPROFEN (Orudis, Orluvail)
   - NAPROXEN (Naproyn, Naprosyn-SR, Synflex, Noflam, Naxen, Naprosic)
   - DICLOFENAC (Apo-Diclo, Cataflam, Voltaren, Flameril, Diclax)
   - SULINDAC (Clinoril, Aclin, Daclin)
   - TIAPROFENIC Acid (Surgam)
   - MEFENAMIC ACID (Ponstan)

   This group of drugs helps to relieve pain as well as inflammation. They work quickly within a day and also help to relieve stiffness. They may be stopped and started as necessary according to the severity of your symptoms. There is a wide variation in patients’ response to the different NSAIDs. Some patients may find one NSAID helpful, while another patient may find it unhelpful and develop adverse effects, and vice versa.

   The main adverse effect of NSAIDs are gastrointestinal in nature. They increase the risk of peptic ulcers and gastrointestinal bleeding between two and four fold. They may also cause dyspepsia, nausea, heartburn and diarrhoea without causing any peptic ulcers. Sometimes the gastrointestinal adverse effects can be avoided by the patient taking concurrent gastro-protective medications such as Omeprazole (Losec), Pantoprazole (Somac) or Misoprostol (Cytotec).
3. COXIBS or COX-2 SPECIFIC INHIBITORS (a group of NSAIDs without an increased incidence of upper gastrointestinal complications compared to Placebo (sugar pills).

- CELECOXIB (Celebrex)
- ETORICOXIB (Arcoxia)

These groups of drugs are like the group above, i.e. they relieve pain as well as inflammation. They are not currently funded by PHARMAC and can cost approximately $60 per month, if taken regularly. They are much safer than the older NSAIDs as above, and they have been proven not to show an increased risk of peptic ulcers compared to placebo treatment during research trials. On the whole, they are not anymore effective than NSAIDs, but it is important to bear in mind that there is a wide variation of patients’ response to NSAIDs and Cox-2 specific inhibitors.

MELOXICAM (Mobic) is another NSAID that has been shown to have a reduced risk of peptic ulcers compared to the older NSAIDs such as Diclofenac and Naproxen but it has not been studied against placebo.

The Cox-2 specific inhibitors work quickly and can help to relieve pain and inflammation within hours, or a day of starting treatment. They may be stopped or started as necessary according to severity of your symptoms.

4. CORTICOSTEROIDS (Steroids)

The type of steroids used in rheumatoid arthritis are the type that are used to relieve inflammation and do not have any effect in building up muscles. They may be given directly into a joint using an injection, or may be given systemically using an intravenous route (i.e. via a blood vessel), intramuscularly (i.e. an injection into the muscles) or orally. The oral preparation used in rheumatoid arthritis is PREDNISONE. If you are on regular oral Prednisone, you should not change the dose without your Doctor’s knowledge. You should consider carrying a steroid card stating the dose you are on, and show this to a Doctor in the case of accident or surgery, including the Dentist.

Although steroids are very effective in suppressing rheumatoid arthritis, they have multiple adverse effects such as increase in high blood pressure, tendency towards diabetes mellitus, thinning of the skin and easy bruising, thinning of the bones (osteoporosis), suppression of the immune system and tendency towards infections, fluid retention, cataracts, diabetes, hypertension etc. Therefore corticosteroids should only be used with the lowest possible dose for the shortest duration. To avoid steroid adverse effects, it is my practise to use intramuscular steroid injections (Kenacort) or steroid injections into joints as necessary rather than regular daily oral doses of Prednisone. Giving corticosteroids this way means the patient only gets it if and when she really needs it. If a patient needs regular doses of intramuscular Kenacort or daily doses of Prednisone, it is important that he or she takes medications for prophylaxis against steroid-induced osteoporosis. If a patient is on a daily dose of corticosteroids, the period of greatest bone loss is in the first six months of treatment.
5. SLOW ACTING ANTIRHEUMATIC DRUGS (SAARDs), DISEASE MODIFYING ANTIRHEUMATIC DRUGS (DMARDs). SECOND LINE AGENTS

This group of drugs are often effective in controlling the disease process and are given in the hope that they will put the rheumatoid arthritis into partial or complete remission, and are therefore known sometimes as Disease Modifying Anti-Rheumatic Drugs (DMARDS). They do not work immediately and may take between 1-3 months before the patient notices any benefit. As a result of this delay, they are also known as Slow-Acting Anti-Rheumatic Agents (SAARDS). It is important that patients attend for regular monitoring when they are on these medication for possible side-effects. The monitoring tests are usually blood tests and urine tests.

- HYDROXYCHLOROQUINE (Plaquenil)
- SODIUM AUROTHIOMALATE (Myocrisin ‘Gold’ injections)
- SULPHASALAZINE (Salazopyrin-EN)
- METHOTREXATE (Ledertrexate, Methoblastin)
- CYCLOSPORIN-A (Sandimmun Neoral)
- LEFLUNOMIDE (Arava)

There are other medications that also belong to this group that are not listed here such as MINOCYCLINE and AZATHIOPRINE because they are rarely used in the treatment of rheumatoid arthritis. These drugs are now often used in combination when one drug on its own does not control rheumatoid arthritis sufficiently well. The effectiveness of some of the above medications are dose-related, i.e. more effective with a higher dose. Following an increase in the dosage of the above medications, there is usually a need to increase the frequency of the monitoring blood tests for a while, to look for possible adverse effects. Most of the adverse effects of the above medications tend to appear within the first six months, and it is rare to still get adverse effects from the above medications after a patient has been stabilised on them for a year to two years, but it is still possible, so it is still necessary to get regular monitoring tests done for safety reasons.

6. BIOLOGICAL AGENTS

TNFα INHIBITORS (inhibition of Tumour Necrosis Factor α)

- ETANERCEPT (Enbrel), funded by PHARMAC from 1-11-2010.
- INFLIXIMAB (Remicade)
- ADALUMIMAB (Humira), funded by PHARMAC since 1.1.2006.
- CERTOLIZUMAB PEGOL (Cimzia).
- GOLIMUMAB (Simponi which is the humanised form of Infliximab).
INTERLEUKIN 1 RECEPTOR ANTAGONIST (IL-1Ra)
- ANAKINRA (Kineret)

INTERLEUKIN-6 RECEPTOR ANTAGONIST
- TOCIILIZUMAB (Actemra).

T-CELL ACTIVATION INHIBITOR
- ABATACEPT (Orencia)

B-CELL MATURATION INHIBITOR
- RITUXIMAB (Mabthera), which will be funded by PHARMAC from 1-7-13.

Thanks to the biotechnological revolution, the above biological agents are specially manufactured for the treatment of inflammatory arthritis such as rheumatoid arthritis. They have come about as a result of two-three decades of medical research. They are like “smart bombs”, targeting the inflammatory cells and processes in rheumatoid arthritis with little collateral damage (i.e. little adverse effects). On the whole, they are much more effective than our traditional slow-acting anti-rheumatic drugs under Group 5 with a much lower incidence of adverse effects to date. The first two (Etanercept and Infliximab) have only been commercially available since November 1998. Anakinra has become available since November 2001, and Adalimumab since 2002. They are currently prohibitively expensive, costing approximately NZ$15,000 per year just for the medications. However, as more and more become available, the cost of these agents will come down because of competition, and when they are out of the ‘patent’ period.

We have been successful in getting Leflunomide (Arava) funded by PHARMAC in New Zealand since 1-5-2002. Humira (Adalimumab) has been available since 1-1-06, and Etanercept (Enbrel) since 1-11-10. Adalimumab and Etanercept are available for the treatment of rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis and ankylosing spondylitis under very strict criteria. The New Zealand Rheumatology Association and Arthritis New Zealand continue to lobby for more of these biological agents to be funded in New Zealand by PHARMAC.

Timaru is a centre for trialing new anti-rheumatic therapies in randomised, placebo-controlled studies with long-term extensions. There are currently several new therapies in phase III (final trials prior to approval by FDA) clinical development for inflammatory rheumatic diseases, and some of these trials are carried out in Timaru. During the past few years, we have seen the advent of small molecule entities (SMEs) or immunomodulators which are given orally and are as effective as the biologics listed above. The first of the SMEs, Tofacitinib (Xeljanz) was approved by the FDA for the treatment of Rheumatoid Arthritis on 7-11-12.

Medications belonging to groups 4, 5 and 6 above should not be stopped and started according to symptoms, without medical supervision.

D.W.T. CHING, MBChB, FRCP, FRACP,
CONSULTANT RHEUMATOLOGIST,
April 2013
TIMARU HOSPITAL.