Early diagnosis and treatment of rheumatoid arthritis

Current management of rheumatoid arthritis is focused on early referral, diagnosis and treatment, with the aim of achieving early disease remission and thereby limiting joint damage and functional disability.

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Rheumatoid arthritis affects approximately 1% of Australians. It is a chronic, systemic, inflammatory disease involving the synovial joints that, over time, results in erosive joint damage. Until recently, 50% of patients with rheumatoid arthritis were unable to work due to their disability 10 years after the onset of disease. Average life expectancy was also reduced, by up to 10 years, as a result of an excess in cardiovascular mortality. With the focus today on early diagnosis, early referral and early introduction of disease modifying antirheumatic drugs (DMARDs) – as well as management of vascular risk factors – it is likely that comparable figures in the future will be more favourable.

A case study: introducing Naomi

Naomi, a 21-year-old woman, presents to you with a three-week history of increasing stiffness and pain involving her shoulders, hands, wrists, ankles and feet. She is employed in a childcare centre and is finding it difficult to work – especially in the mornings, which is when her symptoms are worst. She has been taking paracetamol intermittently, which helps a little. She describes a recent sore throat that improved over a few days with no treatment.

Naomi has previously been well with no medical problems. She mentions having an aunt with 'bad arthritis'. She admits to smoking more, up to 20 cigarettes/day since her symptoms began.

Who gets rheumatoid arthritis, and why?

Rheumatoid arthritis seems to occur more often in women than men, in a ratio of 3:1.[1] The age of onset varies, peaking between 20 and 40 years for women but often occurring in the sixth to eighth decade for men.[2] The incidence of rheumatoid arthritis is higher in Caucasian populations than in indigenous Australian and Asian populations.[3,4]

Up to 70% of rheumatoid arthritis may be related to genetic factors. Patients express a 'shared epitope' (an identical short amino acid sequence) of leucocyte antigens (including HLA-DR1, HLA-DR4 and HLA-DR10) more commonly than the general population. This shared epitope seems to be associated with more severe disease. Environmental factors such as smoking and infections may also play a role.

Rheumatoid arthritis is a chronic inflammatory disease of the synovium that is orchestrated by a number of cell types, including T-cells and B-cells,

IN SUMMARY

- **Early referral, early diagnosis and early introduction of disease modifying antirheumatic drug (DMARD) therapy can improve the course of rheumatoid arthritis.**
- **DMARD therapy, with the aim of reducing joint inflammation, can prevent joint damage and limit functional disability.**
- **Regular monitoring of disease activity and for drug toxicity is important.**
- **Screening and management of vascular risk factors and osteoporosis are necessary in patients with rheumatoid arthritis.**
- **Patient education and support are crucial in management.**

Table 1. Some extra-articular manifestations of rheumatoid arthritis

General
Fever
Lymphadenopathy
Weight loss
Lethargy
Pulmonary
Interstitial fibrosis
Pleural disease
Nodules
Bronchiolitis obliterans
Cardiac
Pericarditis
Myocarditis
Coronary vasculitis
Dermatological
Nodules
Vasculitis
Ocular
Scleritis
Episcleritis
Nodules (choroid, retinal)
Neurological
Entrapment neuropathy
Peripheral neuropathy
Mononeuritis multiplex
Haematological
Felty's syndrome (rheumatoid arthritis, splenomegaly, neutropenia)
Large granular lymphocyte syndrome
Lymphoma
Other
Sjögren's syndrome
Amyloidosis

and their products, such as cytokines. Some of the cytokines produced include tumour necrosis factor (TNF), interleukin-1 (IL-1), chemokines and prostanoids. This inflammatory response results in joint destruction, with erosion of bone as well as ligament and tendon damage.

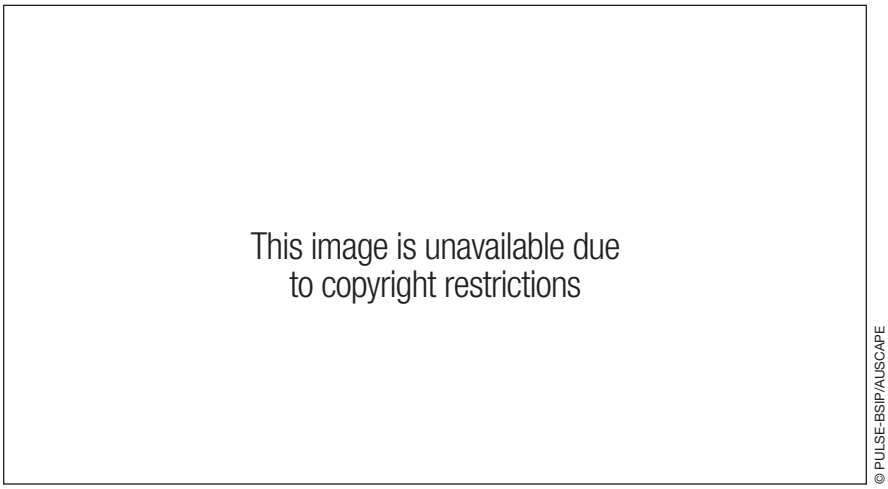

Figure 1. Symmetrical distribution of synovitis involving the metacarpophalangeal and proximal interphalangeal joints of the hands in a patient with rheumatoid arthiritis.

Naomi's clinical findings

On examination, Naomi looks tired. Her blood pressure is 130/70 mmHg and her temperature 36.4°C. There is symmetrical tender soft tissue swelling of her knuckles, wrists and proximal interphalangeal joints. She can form a fist with both her hands but it is painful for her to do so. She is able to walk with difficulty on similarly swollen ankles and feet. She has difficulty raising her arms above her head due to shoulder pain.

There are no associated rash or nail changes. Her oropharynx is not inflamed, and examination of other systems is unremarkable.

Clinical features of rheumatoid arthritis

Rheumatoid arthritis can affect any synovial joint. Most patients complain of symmetrical pain, swelling and stiffness of the small joints of the hands and feet first, classically the metacarpophalangeal, proximal interphalangeal and metatarsophalangeal joints (while sparing the distal interphalangeal joints). An example is shown in Figure 1. Involvement of the larger joints occurs later. Symptoms are often worst in the morning; this is an important feature of inflammatory arthritis.

Not all patients have this classic presentation, particularly early in their disease. A migratory, palindromic or oligoarticular joint involvement may precede the development of a symmetrical small and large joint arthritis.

As rheumatoid arthritis is a systemic inflammatory disease, fever, weight loss and fatigue can occur. Rheumatoid nodules occur in 25% of patients, who usually also have rheumatoid factor positivity. Rheumatoid nodules arise most commonly over pressure points, such as the extensor surfaces of the forearms, but they can occur anywhere. Involvement of the lungs and other organs can also occur (Table 1).

Naomi's investigations

You arrange some blood tests for Naomi, which show:

- haemoglobin 118 g/L (normal range, 130 to 180 g/L)
- white cell count $10x10^9$/L (3.5 to $11x10^9$/L), normal differential
- platelets $490x10^9$/L (150 to $450x10^9$/L)
- creatinine 72 µmol/L (60 to 110 µmol/L)
- liver function tests within the normal range.

Naomi's inflammatory markers are

Table 2. Features in early inflammatory arthritis suggesting a diagnosis of rheumatoid arthritis[5]*

Symptom duration of more than six weeks
Early morning stiffness of more than one hour
Arthritis in three or more regions
Bilateral compression tenderness of metacarpophalangeal or metatarsophalangeal joints
Symmetry of the areas affected
Rheumatoid factor positivity
Anti-cyclic citrullinated peptide (anti-CCP) antibody positivity
Bony erosions evident on radiographs of the hands or feet, although these are uncommon in early disease

* Reproduced with permission from: Rheumatology Expert Group. *Therapeutic Guidelines: Rheumatology*. Version 1. Melbourne: Therapeutic Guidelines; 2006. p.66.

Table 3. Important differential diagnoses for rheumatoid arthritis

Cause	Clues
Viruses (including hepatitis B and C, HIV, Epstein–Barr virus, Ross River virus, Barmah Forest virus, parvovirus, rubella virus)	Symptom duration <3 months Occupational, travel history Risk factors for sexually transmitted diseases
Reactive arthritis	Recent sore throat Diarrhoea Urethral symptoms Uveitis Risk factors for sexually transmitted diseases (e.g. chlamydia, gonorrhoea infection) 'Sausage digits' (dactylitis)
Systemic lupus erythematosus	Hair loss Mouth ulcers Raynaud's phenomenon Photosensitive rash Neurological symptoms (e.g. seizures)
Psoriatic arthritis	Psoriasis, or family history of psoriasis Nail changes Dactylitis
Tophaceous gout	Excessive alcohol intake Flares of pain episodic and related to alcohol, high purine intake Use of diuretics, cyclosporin
Pseudogout (calcium pyrophosphate deposition)	Episodic flares of pain Calcification of articular cartilage (chondrocalcinosis) on x-ray
Primary generalised osteoarthritis	Distal interphalangeal involvement Family history of osteoarthritis Hard 'bony' (not soft tissue) swelling

elevated, with erythrocyte sedimentation rate (ESR) 67 mm/hour (0 to 14 mm/hour) and C-reactive protein (CRP) 50 mg/L (<3 mg/L). Rheumatoid factor is not detectable, and antinuclear antibody titre is 1/40, homogenous pattern. Plain x-rays of the hands and feet show some soft tissue swelling, but otherwise the bones and joints look normal.

You call a local rheumatologist and arrange an urgent review for the following week. You advise Naomi to take regular ibuprofen until her appointment.

Diagnosis

As with most autoimmune disorders, there is no single clinical, serological or radiological test for rheumatoid arthritis. The diagnosis relies on the combination of these features, and is largely a clinical one. It can be difficult to discern a self-limiting viral arthritis from rheumatoid arthritis, especially in the early stages. It is possible that Naomi's inflammatory polyarthritis may be due to parvovirus infection, particularly as she works in a childcare centre. She could also have a post-streptococcal reactive arthritis as she had a preceding sore throat, although it is more common for this to present with asymmetrical joint involvement. Time will help elucidate these causes. Parvovirus related arthritis is usually self-limited with symptoms resolving by six weeks.

Early morning stiffness and the other features listed in Table 2 are suggestive of rheumatoid arthritis. The use of anti-cyclic citrullinated peptide (anti-CCP) antibody testing and MRI may also assist in differentiating early rheumatoid arthritis from other forms of inflammatory polyarthritis (see below). Some of the differential diagnoses that should be considered are listed in Table 3.

Investigations

Laboratory tests

Laboratory findings may reveal an anaemia of chronic disease – often with a

thrombocytosis, as in Naomi's case. The white cell count may be normal, elevated or depressed (such as in Felty's syndrome). An inflammatory response, with elevated ESR and CRP, is common and, if persistent, is associated with increased erosions and mortality.

Rheumatoid factor (RF) is antibody directed against the Fc portion of immunoglobulin G. As a diagnostic test, the use of RF is limited because it is found at presentation in only half of patients with rheumatoid arthritis (a further 35% of patients become positive six months after diagnosis). To complicate matters further, a low titre positive RF is found in 3% of young healthy people, a proportion that increases to 25% with age.[6] Other causes for RF positivity are listed in Table 4. As such, a positive RF should always be interpreted in the clinical context. There is evidence that a high titre is associated with extra-articular manifestations and more aggressive, erosive disease.[8]

Anti-CCP is a more useful test in early inflammatory arthritis. Citrulline is a target amino acid from filaggrin, which is found in skin. ELISAs that detect antibodies to citrulline have high sensitivity (47 to 76%) and specificity (90 to 96%) for rheumatoid arthritis.[9,10]

Anti-CCP and RF may be present years before the onset of joint symptoms. There is some evidence that patients with early arthritis who are anti-CCP positive are at greater risk of progressive and more rapid erosive disease.[11]

Table 4. Some causes of rheumatoid factor positivity[7]*

Age greater than 60 years

Rheumatic diseases
Rheumatoid arthritis
Sjögren's syndrome
Systemic lupus erythematosus

Viral infections
Hepatitis C (with cryoglobulins)
Hepatitis B
HIV infection
Parvovirus infection
Influenza

Bacterial infections
Endocarditis
Osteomyelitis
Tuberculosis

Chronic inflammatory conditions
Inflammatory bowel disease
Sarcoidosis
Pulmonary fibrosis
Primary biliary cirrhosis

Malignancy

* Adapted from reference 7. O'Dell JR. Rheumatoid arthritis. In: Imboden J, Hellman DB, Stone JH. Current rheumatology diagnosis and treatment. New York: McGraw-Hill; 2004. p. 151.

Radiology

It is not surprising that Naomi's x-ray is relatively normal, apart from the soft tissue swelling, as erosions on plain x-ray are found only in 15 to 30% of patients with rheumatoid arthritis one year after disease onset. The earliest erosions are usually juxta-articular and occur most frequently in the feet and the ulnar styloid. Periarticular osteopenia can also occur. It is worthwhile obtaining films of both wrists, hands and feet annually to assess the progression of disease (Figure 2).

MRI is more sensitive than x-ray in detecting erosions, and can do so as early as four months from symptom onset.[11] The presence of bone oedema on MRI may also be predictive of erosive disease.[12] With ultrasonography using colour and power doppler modes, it is possible to detect synovitis in patients with minimal joint swelling. These imaging modalities are not indicated as part of the routine investigation of patients with early arthritis, but may be useful for rheumatologists in cases of diagnostic difficulty.

Naomi's progress

Naomi's joint pain and swelling continue despite ibuprofen. She is reviewed by a rheumatologist, who agrees that she has an early inflammatory arthritis and performs further tests. These include viral serology (including parvovirus, hepatitis B and C) and a throat swab for *Streptococcus pyogenes*, which are noncontributory. Naomi's anti-CCP is elevated – over 250 U/mL (0 to 7 U/mL). A chest x-ray is normal. She is not pregnant.

Treatment with prednisone (10 mg/day) is commenced, and she is booked to return in a few weeks with a view to commencing methotrexate if her arthritis continues. She is strongly encouraged to cease smoking.

Early referral, diagnosis and treatment

Limiting joint damage and functional disability by aiming for disease remission is the goal of long term management in patients with rheumatoid arthritis.

Figure 2. Plain radiograph of right hand showing damage associated with rheumatoid arthritis, including erosive changes at the wrist and metacarpophalangeal joints. There is ulnar deviation of the metacarpophalangeal joints and periarticular osteopenia.

Urgent referral – within eight to 12 weeks – is crucial for early initiation of disease-modifying therapy. There is now evidence from several randomised controlled trials to suggest that the best outcomes result from early diagnosis and early initiation of DMARDs.[13,14] The current view is that there exists a 'window of opportunity' between symptom onset and radiological damage, usually less than three months, during which it is possible to alter the course of rheumatoid arthritis (Figure 3).[15] Patients who commence traditional DMARDs (e.g. methotrexate) early have decreased joint damage and better long term outcomes and quality of life than those who delay treatment by as little as three months.[13-16] DMARDs are of benefit later on in rheumatoid arthritis also, but this benefit may not be as marked.

Management

The management of a patient with rheumatoid arthritis requires a multidisciplinary approach that includes the GP and rheumatologist, as well as physiotherapists, occupational therapists and other allied health practitioners. It involves ongoing assessment of disease activity, complications and treatment-related toxicity. An approach is outlined in the flowchart on page 48. Continuing patient education and support are very important.

Symptomatic treatment

Initial management includes the use of anti-inflammatories to reduce pain. Prednisone (Panafcort, Predsone, Sone) or prednisolone (Panafcortelone, Predsolone, Solone) is very useful as a short term treatment to reduce pain and swelling; it is usually initiated at a dose of 10 to 15 mg/day, depending on comorbidities.

Traditional DMARDs

Disease remission can be defined as symptomatic relief, absence of joint swelling and normalisation of inflammatory markers. Remission can be achieved in 50% of patients with rheumatoid arthritis. There are many DMARDs available (Table 5);[17-35] the choice will depend on the severity of disease as well as age, comorbidities and prognostic factors.

Our patient, Naomi, has rheumatoid arthritis of moderate severity with some functional impairment. She also has several worrying prognostic factors: onset in early adulthood, multiple joint involvement (>20 joints), elevated inflammatory markers, and anti-CCP positivity. These support a more aggressive approach to DMARD therapy. It would be reasonable to commence Naomi on methotrexate (Ledertexate, Methoblastin), and to titrate to the maximum tolerated dose. Methotrexate begins to have an effect within two to six weeks, and prednisone can be weaned during this period as methotrexate becomes increasingly effective.

For patients who do not respond to monotherapy, there is evidence from multiple randomised controlled trials supporting a 'step up' approach, with the addition of a second and/or third DMARD. There are also results from some trials that suggest initial combination DMARD therapy may be better than monotherapy in inducing remission and reducing joint damage.[36] For patients with very active disease, combination therapy may be started early – in particular, triple therapy with methotrexate sulfasalazine (Pyralin EN, Salazopyrin) and hydroxychloroquine (Plaquenil). Patients in the trials seemed to tolerate the combination regimens as well as those on monotherapy, with no increase in toxicity. In patients who are intolerant of methotrexate, leflunomide (Arabloc, Arava) is an effective and well tolerated monotherapy. It is also useful in combination with methotrexate.

The 'best' DMARD regimen is not clear, so decisions must be tailored to the patient. More detailed discussion of these trials is beyond the scope of this article; readers are referred to the American College of Rheumatology's 2002 management guidelines for a summary.[37]

Biological DMARDs

If remission is not achieved with appropriate use of traditional DMARDs then biological agents should be considered. There are three anti-tumour necrosis factor (anti-TNF) agents and one IL-1 receptor antagonist available for treating rheumatoid arthritis in Australia:

- infliximab (Remicade), a chimeric human–mouse monoclonal antibody against TNF given by intravenous infusion every eight weeks
- etanercept (Enbrel), a recombinant fusion protein composed of the TNF receptor and the constant portion of human IgG1 given by subcutaneous injection once or twice a week
- adalimumab (Humira), a fully human

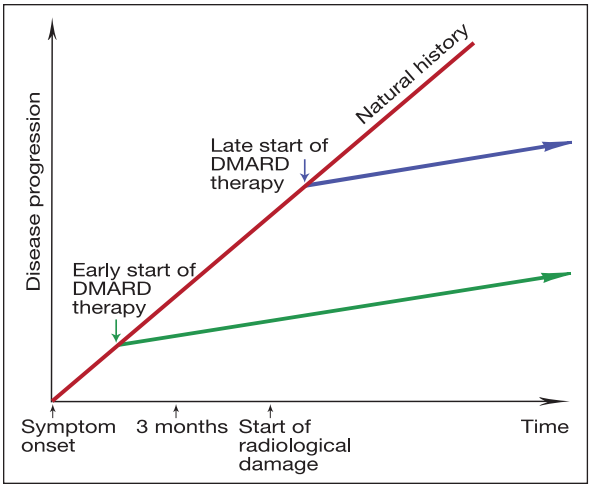

Figure 3. Altering the course of rheumatoid arthritis. Starting traditional DMARD therapy earlier – within three months of symptom onset – is associated with better long term outcomes than starting later.[16]

monoclonal TNF antibody given subcutaneously once a fortnight
- anakinra (Kineret), a recombinant IL-1 receptor antagonist given subcutaneously daily.

In order to qualify for these drugs under the PBS, patients must meet strict criteria, including a specified number of tender and swollen joints, raised inflammatory markers and treatment failure of multiple DMARDs.

TNF is an important cytokine in the pathogenesis of rheumatoid arthritis. It is produced by monocytes and macrophages and has multiple effects on the inflammatory cascade, including stimulation of release of other cytokines, production of matrix metalloproteinases, and suppression of cartilage proteoglycans. These and other actions play a major role in joint destruction in rheumatoid arthritis. Anti-TNF agents directly bind to TNF before it can bind to its cell surface receptors and exert its effects. Anakinra works by blockade of the receptor of IL-1, a proinflammatory cytokine.

All three anti-TNF agents have been shown to be effective in early and established rheumatoid arthritis, both as monotherapy and – more effectively – in combination with methotrexate. These agents and anakinra seem to slow radiographic progression, suggesting long term disease modification. There have been no trials comparing these agents head-to-head, but an indirect comparison of the three anti-TNF agents has suggested similar efficacy.[38] Anakinra is also effective, perhaps to a lesser extent than the anti-TNF agents, in rheumatoid arthritis.

An approach to rheumatoid arthritis in general practice

Patient with possible rheumatoid arthritis

(e.g. pain in multiple joints, early morning stiffness, bilateral compression tenderness in metatarsophalangeal or metacarpophalangeal joints)

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Aim to establish diagnosis early

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- Take a detailed history, including family history
- Perform a thorough examination – look for actively inflamed joints, extra-articular manifestations
- Arrange tests as appropriate – full blood count, electrolytes, liver function, ESR, CRP, rheumatoid factor, anti-CCP, baseline x-rays of hand and feet, chest x-ray

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If rheumatoid arthritis is likely:
- arrange early referral for rheumatological assessment and, if diagnosis is confirmed, early initiation of DMARD therapy
- consider use of anti-inflammatory and/or prednisone or prednisolone for symptom relief

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Participate in ongoing management for rheumatoid arthritis, such as:*
- regular assessments of disease activity, drug efficacy and toxicity
- screening, as appropriate (e.g. cervical Pap smears)
- monitoring for cardiovascular risk factors, and treatment as necessary
- screening for osteoporosis (particularly if long term glucocorticoids are used)
- continuing patient education and support

* Conducted in conjunction with other healthcare professionals, including a rheumatologist, physiotherapist and occupational therapist.
Abbreviations: ESR = erythrocyte sedimentation rate, CRP = C-reactive protein, anti-CCP = anti-cyclic citrullinated peptide antibody.

Prescribing considerations

The biological DMARDs and some of the traditional DMARDs (e.g. methotrexate, leflunomide, cyclosporin [Cicloral, Cysporin, Neoral, Sandimmun]) predispose patients to infection. These include common infections such as pneumonia and also opportunistic infections, such as herpes zoster and listeriosis. GPs and patients need to be vigilant, as signs of infection are often subtle or absent given that these agents modify the usual 'inflammatory' warning signs. Patients should be advised to seek medical advice if febrile or unwell and to cease biological DMARD therapy until any infection has been treated.

Table 5. DMARDs for rheumatoid arthritis: efficacy, safety and monitoring principles[17]*

	Efficacy		Frequency of major toxicity[18]	Usual routine monitoring[18]
	In monotherapy	With methotrexate		
Traditional DMARDs				
Methotrexate (Ledertrexate, Methoblastin)	++[19]	–	+	Monthly: full blood count, liver function tests
Sulfasalazine (Pyralin EN, Salazopyrin)	++[20]	+++[21,22]	+	Monthly: full blood count, liver function tests
Hydroxychloroquine (Plaquenil)	+[23]	++[21]	–	Six- to 12-monthly: retinal examination
Leflunomide (Arabloc, Arava)	++[24]	+++[25]	+	Monthly: full blood count, liver function tests
Intramuscular gold (Myocrisin)	++[26]	+++[27]	++	Monthly: full blood count, urinalysis
Cyclosporin (Cicloral, Cysporin, Neoral, Sandimmun)	++[28]	+++[29]	++	Monthly: full blood count, electrolytes and creatinine, liver function tests, blood pressure measurement
Azathioprine (Imuran)	+[30]	Unknown	+	Monthly: full blood count, liver function tests
Cyclophosphamide (Cycloblastin, Endoxan)	++[30]	Not used	+++	Monthly: full blood count, electrolytes and creatinine, liver function tests, urinalysis
Penicillamine (D-Penamine)	++[31]	Unknown	+++	Monthly: full blood count, electrolytes and creatinine, liver function tests, urinalysis
Biological DMARDs				
Tumour necrosis factor inhibitors – infliximab (Remicade), adalimumab (Humira), etanercept (Enbrel)	++[32]	+++[32-34]	+	Monthly: full blood count, electrolytes and creatinine, liver function tests
Anakinra (Kineret)	+	++[35]	+	Monthly: full blood count, electrolytes and creatinine, liver function tests

* Modified from reference 17. Roberts LJ, Cleland LG, Thomas R, Proudman SM. Early combination disease modifying antirheumatic drug treatment for rheumatoid arthritis. Med J Aust 2005; 184: 122-125.
The +/– scoring is a clinical guide to relative effects representing the views of the authors of reference 17 based on published studies where indicated; +++ represents the maximum efficacy or toxicity.

It has been estimated that patients with rheumatoid arthritis who are taking anti-TNF agents are five times more likely to develop active tuberculosis than matched patients with rheumatoid arthritis.[39] Prior to starting such agents, estimation of tuberculosis risk is mandatory – this requires a careful history, a Mantoux skin test or Quantiferon-TB Gold blood test, and chest x-ray. Patients thought to have latent tuberculosis may need isoniazid prophylaxis.

It is possible that biological DMARDs may increase the risk of malignancies and demyelinating disease, although this has not been proven in large studies. Thus, patients with a recent history of malignancy, demyelinating disease, or active chronic infection should not be given these agents. Anecdotally, skin cancers may be more frequent in patients taking biological DMARDs, so skin protection and regular skin examination is important.

Injection site reactions are common, and usually minor. Infusion reactions with infliximab can also occur. Other effects of anti-TNF agents include autoantibody production, which very rarely manifests clinically as a drug-induced lupus syndrome.

It is crucial that patients with rheumatoid arthritis be seen regularly for monitoring of DMARD therapy and assessment of disease activity (Table 5). Regular screening as appropriate (for example, cervical Pap smears) is also important in this group.

Cardiovascular health and bone health

Patients with rheumatoid arthritis are at increased risk of accelerated atherosclerosis due to the systemic inflammatory nature of their disease. This increase in risk is independent of any traditional vascular risk factors that they may have.

Women with rheumatoid arthritis are at a two to three times increased risk of having a myocardial infarction. It is important that our patient, Naomi, stops smoking and that other vascular risk factors are modified as necessary. There is some evidence that effective control of inflammation reduces cardiovascular mortality.[40]

Screening and management of osteoporosis are also important, particularly for patients who are taking long term corticosteroids.

Other management issues

Outcomes are better for patients with rheumatoid arthritis who exercise – aerobic exercise three times per week, for 30 to 60 minutes, plus strengthening exercise sessions are suggested. Weight loss, if

necessary, improves cardiovascular health and risk of osteoporosis.

The use of fish oil can reduce symptoms and reduce proinflammatory cytokines. The dose required to produce this effect is 0.2 g/kg (about 14 standard 1 g capsules per day or 15 mL of fish oil per day).[41] MT

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DECLARATION OF INTEREST: None.

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