



RECOMMENDATIONS FOR THE USE OF BIOLOGICAL AGENTS FOR THE TREATMENT OF RHEUMATIC DISEASES*

* DISCLAIMER

These recommendations are written to assist Australian rheumatologists prescribing biological agents in rheumatic diseases. They are not Medicare Australia requirements for subsidised prescription but reflect worldwide recommendations for use. They were prepared for members of the Australian Rheumatology Association following initial request by Council with annual update as new data and new agents become available. They represent the views of members of the Therapeutics Committee. These recommendations are non mandatory, for educational purposes only and subject to continuing change.

INTRODUCTION

Rheumatoid Arthritis (RA), Juvenile Idiopathic Arthritis (JIA), Ankylosing Spondylitis (AS) and Psoriatic Arthritis (PsA) are common inflammatory rheumatic diseases in Australia affecting over 750,000 men, women and children. These diseases not only cause persistent pain, loss of quality of life, significant disability and loss of employment for many patients, but also accrue ongoing costs for the Australian community.

Goals for treatment include prevention of disability and either clinical disease remission or tight control of disease activity if remission is not possible. The mainstays of treatment were exercise, local corticosteroid injections, non-steroidal anti-inflammatory drugs (NSAIDs) and conventional disease-modifying anti-rheumatic drugs (DMARDs) including methotrexate (MTX) used alone or in combination.

The addition of biological agents or bDMARDs have revolutionised the management of these diseases and improved the lives of many patients. Biological agents may either reduce immune cell activity or selectively block cytokines found in excessive amounts in blood and joints of people with RA, JIA, AS and PsA. Their use must take into account cost; drug availability; patient preferences and co-morbidities, their disease characteristics predictive of rapid progression, and previous response to therapies including drug toxicity.

Until long term safety is better defined usage continues to need to be circumspect. The potential risk versus benefit needs to be individualised for each patient. Hence the prescription of biological agents requires rheumatologists experienced in the diagnosis, treatment and assessment of RA, JIA, AS and PsA.

TNF INHIBITORS

Three TNF inhibitors are available for prescription by Australian rheumatologists:

1. Etanercept is a human TNF receptor fusion protein which binds to both free TNF and lymphocytotoxin α preventing them from activating cell surface TNF receptor. Etanercept has a half life of 2.9 days and is given as a subcutaneous injection either 50mg once weekly or 25 mg twice weekly (3-4 days apart) for RA, AS, PsA and polyarticular JIA (0.4mg/kg to maximum 25mg twice weekly dose).
2. Adalimumab is a human recombinant monoclonal antibody which binds to TNF- α and blocks interaction with the p55 and p75 cell surface TNF receptors. The half life is 8-9.5 days and dose is 40 mg subcutaneous injection fortnightly for RA, AS and PsA.
3. Infliximab is a chimeric part mouse/part human monoclonal antibody which binds to the soluble and transmembrane forms of TNF- α , thereby blocking binding of TNF- α with its receptors. The half life is 14 days. The treatment regimen is by infusion at 0, 2, and 6 weeks then 8 weekly for RA (at dose 3 mg/kg) whilst for AS and PsA then 6-8 weekly (at dose 5mg/kg).

Patient choice of agent is often based on individual characteristics, choice for route of administration and availability of infusion centres. As they differ in protein source, mechanism of action and pharmacokinetics, there is scientific as well as clinical rationale for trying an alternative TNF inhibitor in the same patient who has demonstrated lack of efficacy or toxicity to one TNF inhibitor. There is also now some evidence that TNF inhibitor use in RA, AS and PsA are cost effective from healthcare resource utilisation.

Rheumatoid Arthritis (RA)

INDICATIONS

1. Established severe active RA.
2. Persistent symptoms and signs of poorly controlled and active disease defined as 6 or more swollen and tender joints, or 4 non-hand joints, or a DAS 28 score ≥ 3.2 .
3. Failed adequate therapy with 2 standard DMARDs of which MTX must have been one (and others include sulfasalazine, leflunomide, cyclosporin, hydroxychloroquine or intramuscular gold). DMARDs including MTX should have been given for at least 3-6 months with at least 2 months at standard target dose (eg. MTX 20-25mgs per week) unless limited by toxicity or intolerance.

Although adalimumab and etanercept are both approved as mono therapy for RA whereas infliximab is approved with MTX in RA, several studies indicate that neither one agent is more effective than another and that the combination of each TNF inhibitor with another DMARD usually MTX is associated with superior efficacy (eg ACR70, EULAR remission) and less radiological progression.

It will be rare in clinical practice that circumstances necessitate use of TNF inhibitors in DMARD naïve patients.

RESPONSE

Rheumatologists are encouraged each visit to record components of a DAS28 which simply involves a Patient Global VAS with swollen and tender joint counts and an acute phase reactant (either ESR or CRP). Improvement should occur by 12-16 weeks for a TNF inhibitor responder.

1. Lack of response assessed between 12-16 weeks is defined as failure to reach DAS28 < 3.2 or to improve by > 1.2 from baseline DAS28 score. However if other changes in therapy have occurred (for example treatment has allowed reduction in steroid dose), treatment may continue but should not be maintained for more than 6 months if the DAS28 responses are not achieved (See APPENDIX 1.)

or

2. Lack of response is defined as failure to reach ACR 20 response at 12-16 weeks ie. 20% reduction in each of swollen and tender joint counts and a 20% improvement in at least 3 of the following: Patient Global assessment (100mm VAS), Patient Pain (100 mm VAS), Physician Global assessment (100 mm VAS), acute phase reactant (either ESR or CRP) and patient self-assessed disability measure e.g., mHAQ or SF36 questionnaires.

Treatment failure including loss of response or adverse effects is observed in up to one-third of patients on TNF inhibitors for RA. Options to provide additional response include adding in or increasing dosage of conventional DMARDs, increasing the dose or reducing the dosing intervals for infliximab and Adalimumab, switching to a second TNF inhibitor, or switching to another class of biological agent.

Ankylosing Spondylitis (AS)

INDICATIONS

TNF inhibitors should be given to AS patients with persistently high disease activity (BASDAI ≥ 4) who have failed conventional treatments according to ASAS recommendations (See APPENDIX 2). To date randomized controlled trials (RCTs) of these drugs have enrolled patients who have satisfied the modified New York plain x-ray classification criteria for AS, including x-ray confirmed sacroiliitis (similar

to the requirement necessary for Medicare Australia subsidisation). With the increasing availability of MRI and thus ability to diagnose as at an earlier stage it is hoped trial evidence will confirm the benefit of treatment for these MRI positive patients. HLA B27 status or raised inflammatory markers (ESR or CRP) are not anti TNF response modifiers. There is no evidence to indicate one TNF inhibitor is more effective than another. There is little evidence to support the use of conventional DMARDs alone in axial disease.

RESPONSE

Rheumatologists are encouraged at each visit to record with the obligatory Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) a Patient Global (VAS) and AS physical measurements (occiput-wall, chest expansion, lateral spinal flexion, modified Schober test).

Lack of response is defined as failure to reach BASDAI 50% improvement or 2 point improvement of baseline BASDAI when assessed between 6-12 weeks.

Psoriatic Arthritis (PsA)

INDICATIONS

PsA is probably the most heterogeneous rheumatic disease which has approval for TNF inhibitor treatment hence the development of classification criteria and GRAPPA (The Group for Research and Assessment of Psoriasis and Psoriatic Arthritis) treatment guidelines.

TNF inhibitor treatment needs to consider each component of the disease (peripheral joint, dactylitis, enthesitis, spondyloarthropathy, skin, nails)ie., not simply rely on number of swollen and tender peripheral joints as per Medicare Australia subsidised requirement (20 active swollen and tender joint count or at least 4 only using wrist, elbow, shoulder, ankle, knee or hip). Elevation of an acute phase reactant (ESR and / or CRP) is not a TNF inhibitor response modifier.

RCT data to support conventional DMARDs (sulfasalazine, methotrexate, cyclosporin, leflunomide) as first line therapy for PsA remain limited whereas RCTs with the three available TNF inhibitors all show significant responses.

As a result of cost and until long term safety is clearer, TNF inhibitor therapy should be considered in patients with a history of psoriasis, an inadequate response to NSAID's and/or steroid injections, with at least 5 or more swollen and similarly 5 or more tender or painful joints / entheses / dactylitis sites in the setting of psoriatic spondyloarthropathy and after failing adequate methotrexate and /or leflunomide therapy.

RESPONSE

Lack of response is defined as failure to reach ACR 20 response when assessed at 12-16 weeks ie., 20% reduction in each of swollen and tender joint counts and 20% improvement in at least 3 of the following; Patient Pain VAS, Patient Global VAS, Physician Global, mHAQ (or SF 36) or acute phase reactants (ESR or CRP).

POTENTIAL ADVERSE EVENTS

1. Tuberculosis. All TNF inhibitors increase susceptibility to tuberculosis or reactivation of latent (or past) tuberculosis (TB). Screening reduces this risk and is mandatory prior to commencement, using a chest x-ray within last three months, a case history assessment and either two step TST skin test or QuantiFERON TB Gold blood assay. If screening, yields positivity ie., latent TB is possible, TB prophylaxis is recommended (isoniazid 5mg/kg/d, <300mg/d with pyridoxine for 6-9 months OR rifampicin 10mg/kg/d, <600mg/d for 4 months). There is general consensus that TNF inhibitor can be commenced concurrently 4-8 weeks later. Ensure the patient is fully aware of the risks and benefits. Active TB may be clinically atypical (eg extrapulmonary) and TB treatment should involve the local TB expert.

- 2. Other infections.** TNF inhibitors should not be started (or should be discontinued when serious infections occur), until these infections have been adequately treated.
 - a. Septic arthritis (within 12 months)
 - b. Infected prosthesis.
 - c. Acute osteomyelitis.
 - d. Bacterial sepsis or abscess especially in skin and soft tissue
 - e. Systemic fungal or other opportunistic infections especially listeriosis, coccidiomycosis or histoplasmosis.
 - f. Severe bronchiectasis (or recurrent severe chest infections). Can be used with caution in mild to moderate cases.
 - g. Hepatitis. Long term safety for use in hepatitis B and C infection is not known. TNF inhibitor therapy is probably best avoided in the setting of hepatitis B infection as reports are contradictory. There are anecdotal reports of the safety of TNF inhibitor therapy in chronic hepatitis C infection. Pre screening is recommended. Consider each patient risk/benefit aspects.
 - h. HIV. Long term safety is not know. Screen those at risk for this infection.
 - i. Indwelling urinary catheter.
 - j. Chronic cutaneous ulceration. Consider each patient risk/benefit aspects.
- 3. Malignancy.** TNF inhibitors are contraindicated in patients with malignancy within 5-10 years usually until evidence of safety is determined from long term patient registries. Patients should be fully aware of risk / benefit aspects and formal consent is best documented in those with background of malignancy. There is conflicting data whether there is increased risk of lymphoproliferative diseases and solid malignancies. There is evidence that TNF inhibitor therapy increases cancer in RA patients. Patients should be encouraged to stop smoking and until more definitive evidence is available undergo regular skin checks. If potential malignancy is clinically suspected, investigate appropriately and stop TNF inhibitor if malignancy confirmed.
- 4. Demyelinating-Like Syndromes, Multiple Sclerosis, Optic Neuritis, Parkinson's disease** may be no greater than expected in the general population. TNF inhibitors should not be started or should be stopped if these neurological events occur.
- 5. Pregnancy and Lactation.** Advise women to stop prior to and during pregnancy and lactation as insufficient data are available on long term foetal safety.
- 6. Severe Congestive Heart Failure** (NYHA grade 3 / 4). Use with caution in mild to moderate cases.
- 7. Autoimmune-Like Syndromes.** There is increased incidence of several auto antibodies (eg ANAs, dsDNAs) after infliximab which is probably not a class effect. If rare clinical drug-induced lupus, vasculitis and antiphospholipid syndromes develop as a complication this requires TNF inhibitor cessation. Currently there is no evidence that RA patients with positive ANA, dsDNA, and / or anticardiolipin antibodies are at significantly increased risk for development of drug-induced lupus on a TNF inhibitor.
- 8. Injection site / infusion reactions.** Mild to moderate injection site and infusion reactions are common and treated with antihistamine, corticosteroids and slowing infusion rate. Cessation of drug is rarely required.
- 9. Pancytopenia, Aplastic Anaemia.** Requires cessation although rarely reported and usually in context of other diseases and / or causative drugs.
- 10. Psoriatic skin lesions.** New onset psoriasis particularly pustular psoriasis has been reported in patients with RA and AS using TNF inhibitors.

Vaccines

There is a small decrease in the prevalence of adequate protection especially for vaccines given in combination with methotrexate. Live attenuated vaccines (eg., BCG, yellow fever) are not recommended.

Surgical Procedures

There is as yet no consensus on how bDMARDs should be managed in the context of elective surgery. A reasonable approach is to withhold treatment with etanercept for 2-4 weeks prior to major surgical procedures whilst with adalimumab and infliximab 4-8 weeks. Treatment may be restarted post-operatively if there is no evidence of infection and once wound healing is satisfactory.

Laboratory monitoring

Laboratory monitoring helps determine effectiveness of therapy in addition to monitoring the rheumatic disease.

Consider three monthly ESR and CRP, Full Blood Count, Renal and Liver Function tests.

Chest x-ray (pre biologic and post if respiratory symptoms or LTBI follow up, or smoker).

Two Step Tuberculin Skin Test and / or QuantiFERON assay (pre biologic and post if exposure to TB occurs).

Hepatitis B and C serology (pre biologic and annually if appropriate).

HIV screening should be considered in at risk patients.

ANA, DNA (pre biologic and annually).

The frequency and type of tests will also be influenced by usual monitoring requirements for other DMARDs if being used in combination with the TNF inhibitor.

IL-1 INHIBITOR

Anakinra is a recombinant protein which binds to the IL-1 receptor competitively prohibiting IL-1 cytokine production. Anakinra is given as a daily 100 mgs subcutaneous injection in combination with MTX for the treatment of active RA (as per TNF inhibitor recommended indications). Anakinra appears to be highly effective for adult and juvenile onset Still's disease, neonatal onset multi system inflammatory disease (NOMID) Muckle-Wells syndrome and TNF-a associated periodic syndrome (TRAPS).

RESPONSE

As per TNF inhibitors for use in RA.

ADVERSE EVENTS

Adverse events are similar to those described with TNF inhibitors. To date however there is no indication it is associated with an increased incidence of TB. Serious other infections are increased in RA patients. This increased incidence is magnified by corticosteroid use and also combinations with other biological agents. There is an increased incidence of dose related subcutaneous injection site reactions which often do not require treatment.

RITUXIMAB

Rituximab is a chimeric monoclonal anti-CD20 antibody that selectively depletes CD20-expressing B cells. Rituximab does not deplete stem cells, thus allowing new B cells to replete from 6 months. It also does not deplete plasma cells, which make antibodies, allowing a patient's humoral immunity to remain intact.

For rheumatoid arthritis (RA) rituximab is administered by intravenous infusion at dose 2 x 1000mg infusions two weeks apart in an infusion centre with appropriate supportive treatment. Rituximab is usually given with IV 100mg methylprednisolone and oral antihistamine premedication and in combination with ongoing methotrexate. The RA administration regime is different from that used for non-Hodgkin's lymphoma. Rituximab should not be given within 4 weeks of treatment with etanercept or within 8 weeks of receiving adalimumab or infliximab. It should not be given with other biological agents.

Rheumatoid Arthritis (RA)**INDICATIONS**

1. Established severe active RA of >6 months duration whom qualify for treatment with biological agents whom have had an inadequate response to TNF inhibitors. (see RA TNF inhibitor indication section)

2. RA patients whom have an intolerance to TNF inhibitors or serious contraindication to TNF inhibitor use.
3. In combination with methotrexate unless limited by serious toxicity or intolerance. (Efficacy in monotherapy has been shown but the combination with methotrexate does show superior efficacy).
4. Persistent at least moderate disease activity such as DAS28 \geq 3.2, or 6 or more swollen and tender joints, or 4 non-hand joints.

RESPONSE

Rheumatologists are encouraged at each visit to record Patient Global VAS with swollen and tender joint counts and an acute phase reactant. In most cases a response is usually seen by 16 weeks after first infusion.

1. Lack of response assessed between 12-16 weeks is defined as failure to reach DAS28 $<$ 3.2 or an improvement by $>$ 1.2 from baseline DAS28 score.

or

2. Lack of response is defined as failure to reach ACR20 response at 12-16 weeks (see RA TNF inhibitor section).

Failure of response to rituximab does not preclude use of a TNF inhibitor.

REPEAT TREATMENT

Repeat treatment using the same dosing is recommended from 24 weeks following the first infusion based on return of signs and symptoms (eg as measured by an increase in DAS $>$ 1.6 following response) or if there is residual disease (eg as measured by a DAS $>$ 2.6).

Repeat treatment courses are effective in previously responsive RA patients.

POTENTIAL ADVERSE EVENTS

1. **Infusion reactions** are the most frequent adverse events, (fever, chills, shaking, fatigue, tongue swelling, itch, palpitations, chest pain, dyspnoea, myalgia and arthralgia). They are most common with the first infusion (approximately 35%) and reduced with the second infusion (approximately 10%) and subsequent infusions. Intravenous steroid premedication use reduces the incidence and severity of infusion reactions by about 30%. Infusion reaction may require intervention of additional paracetamol, antihistamines, bronchodilator and steroids with slowing the infusion rate. Rarely is withdrawal from rituximab treatment required.
2. **Infections.** Rituximab should not be started or should be discontinued when serious infections occur as for TNF inhibitors. Currently there is no evidence of an increased risk of tuberculosis (TB) in lymphoma patients treated with rituximab. In general, RA patients have been or are on DMARDs including methotrexate and steroids and those whom did not respond to TNF inhibitors will also have been screened for the presence of active or latent TB. Use with hepatitis C is probably safe but hepatitis B and HIV infection are contraindications for use. Progressive multifocal leukoencephalopathy (PML) a rare virus disease of the brain has been reported in a few people given rituximab with SLE.
3. **Malignancy.** To date rituximab has not been associated with increased risk of malignancy in RA patients. If patients have had a previous malignancy treated and cured, it may be reasonable to consider rituximab. RA patients should be encouraged to stop smoking and have an annual skin check.
4. **Demyelinating-Like Syndromes** are not contraindicated to rituximab use. Indeed Rituximab is being trialled in patients with multiple sclerosis.
5. **Pregnancy and Lactation.** Advise women to stop prior to and during pregnancy as insufficient data available on long term safety.
6. **Severe Congestive Heart Failure** (NYHA grade 3 / 4). Use with caution in mild cases.
7. **Late-onset neutropaenia** has been reported in 8% and may occur up to 1 year after treatment. GCSF was required in some of these cases. Most however will also have been on methotrexate.

Vaccines. Owing to B cell depletion, vaccinations to prevent pneumonia and influenza should be given prior to rituximab use then as appropriate although response may then be sub-optimal. Live attenuated vaccines should not be given.

Laboratory monitoring is similar to TNF inhibitor use (minus 2 step TST or Quantiferon assay requirement). Initial immunoglobulin GAM, RF and B cell levels may be done although the latter in routine clinical practice has not proven useful.

Although decreased levels of immunoglobulin (Ig) M, A, G may occasionally be observed with rituximab use, no increase in serious infections were reported in patients with reduced IgM levels after rituximab. TNF inhibitor use in non responsive RA rituximab treated patients who still had B cell levels below normal showed an increase in serious infections.

ABATACEPT

Abatacept selectively modulates a specific co-stimulatory signal required for full T cell activation.

For rheumatoid arthritis (RA) abatacept is administered as a 30 minute intravenous infusion of up to 10mg/kg (500mg for weight less than 60kg; 750mg for weight 60-100kg and 1000mg for weight over 100kg) at 0, 2, 4 weeks then monthly. It should not be given with other biologic agents. The mean half life is approximately 13 days in RA patients and clearance increases with body weight.

Rheumatoid Arthritis (RA)

INDICATIONS

1. Established severe active RA of >6 months duration qualifying for treatment with biological agents (see RA TNF inhibitors indications section) after an insufficient response or intolerance to an adequate trial of methotrexate, another effective DMARD or TNF inhibitor.
2. In combination with methotrexate unless limited by serious toxicity or intolerance.

Abatacept may be substituted directly for the next dose of TNF inhibitor when switching is undertaken.

RESPONSE

Lack of response assessed at 12-16 weeks as per TNF inhibitors and rituximab.

ADVERSE EFFECTS

1. Infections

The risk for activation of latent or new TB is unknown as TB screening and exclusion was done in trials. At present it is felt best to pre-screen all patients and to apply the same hepatitis B and C and HIV screen as per TNF inhibitor protocol. Serious infection rate is increased with abatacept use and similar measures should be applied as per TNF inhibitors. RA patients with COPD had more infective adverse events with abatacept versus placebo use in initial trials.

2. Malignancy. To date the risk of lymphoma is similar to that expected in the RA population. In the initial trials the overall risk of lung cancer was higher than in the general non RA population. Patients should be encouraged to stop smoking and have an annual skin check.

3. Infusion reactions included headache and dizziness but were not a significant problem.

4. Pregnancy and Lactation. Advise women to stop prior to and during pregnancy as insufficient data on long term safety.

APPENDIX 1 DAS28

DAS28 involves the calculation of a 28 joint count for joint swelling and tenderness, determination of the ESR, (or CRP) and Patient Global assessment entered into a formula to give a total score out of 10. Whilst the use of the formula appears cumbersome, a DAS calculator simplifies this.

DAS28 is the preferred objective measurement of disease activity rather than the **ACR20** because the latter measures disease activity in comparison to baseline rather than an overall score which can be used as an entry criteria for treatment nor does it give a ready measure of change in disease activity to assess continuation / stopping criteria.

True Remission: DAS <1.6 or ACR70 response

Remission: DAS <2.6

Low disease activity: DAS 2.6-3.2

Moderate disease activity: DAS 3.2 – 5.1

High disease activity: DAS > 5.1

A change of >1.2 is a significant change in disease activity.

(DAS 28 = 0.56 x square root tender joint count (28 joints *) + 0.28 x square root swollen joint count (28 joints *) + 0.70 log ESR + 0.014 Patient Global (100 mm visual analogue) *shoulders (2), elbows (2), wrists (radiocarpal, carpal and metacarpal = wrist) (2), metacarpophalangeals 1-5 (10), thumb interphalangeals (2), proximal interphalangeals 2-5 (8), knees (2).

APPENDIX 2 ASAS (Assessment in Ankylosing Spondylitis Working Group)**2(a) Disease activity and functional disability measures****BASDAI (Bath Ankylosing Spondylitis Disease Activity Index)**

A composite index made up of 6 questions each measured on a visual analogue scale (VAS) from 0-10cm

1. Fatigue
2. Neck, back or hip pain
3. Pain/swelling in other joints (not neck, back or hip)
4. Overall discomfort from tender areas
5. Overall level of morning stiffness
6. Duration of morning stiffness

BASFI (Bath Ankylosing Spondylitis Functional Index)

A composite index made up of 10 questions, covering basic daily function such as bending and standing, each measured on a VAS (Visual Analogue Scale) from 0-10cm

BASG (Bath Ankylosing Spondylitis Global Score)

A score calculated from two questions which ask patients' to indicate, on a 10cm visual analogue scale, the effect of disease has had on their well-being over the last week and last six months.

Spinal Pain

Level of pain in the back measured on a VAS from 0-10cm

Inflammation/degree of morning stiffness

Mean of Question 5 and 6 of BASDAI.

2(b) Primary and secondary outcome measures for patients with Ankylosing Spondylitis treated with TNF inhibitor therapy.

Primary Outcome	Secondary Outcome
BASDAI 50% improvement	ASAS 5/6 improvement
50% improvement in the BASDAI compared to baseline BASDAI	20% improvement in 5 of 6 ASAS domains without deterioration in sixth domain
ASAS 20% and ASAS 40% improvement	1. Patient global assessment
At least 20% (40%) improvement from baseline and an absolute improvement from baseline of at least 1(2) unit (on scale 0-10) in at least 3 out of 4 ASAS assessment domains	2. Spinal pain
1. Patient global assessment	3. Physical function from BASFI
2. Spinal pain	4. Inflammation/morning stiffness
3. Physical function from BASFI	5. CRP
4. Inflammation/morning stiffness (average last 2 questions BASDAI)	6. Spinal mobility/lateral flexion
And no worsening of >20% (40%) and > 1(2) unit (scale 0-10) in the remaining 1 out of the 4 above domain	ASAS partial remission
	A score of <2 in each of the 4 ASAS 40% improvement domains
	1. Patient global assessment
	2. Spinal pain
	3. Physical function from BASFI
	4. Inflammation/morning stiffness

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Kathie Tymms

Therapeutics Committee, Australian Rheumatology Association

145 Macquarie Street, SYDNEY NSW 2000

Tel: 02 9256 5458; Fax: 02 9256 9692; email: robynm@racp.edu.au