



UPDATED 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 based on best available evidence at the time, or if this is incomplete good clinical practice. 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 some 3% of the population hence over 750,000 men, women and children. These diseases not only cause persistent pain and stiffness but also tissue damage with disability, loss of quality of life and employment all of which accrue ongoing costs for the Australian community.

The goal for treatment is clinical and radiological disease remission with treatment to target strategies or tight control of disease activity (if remission is not possible). Conventional disease-modifying anti-rheumatic drugs (DMARDs) primarily methotrexate (MTX) used alone or in combination excluding AS may provide adequate therapy for some severe JIA, PsA and up to one third of early RA.

The addition of biological agents or bDMARDs have revolutionised the management of these diseases and improved the lives of many patients including those with an inadequate response to MTX. Biological agents may be cell-targeted or selectively block cytokines found in excessive amounts. Their use should take into account cost; drug route access and availability; patient characteristics and co-morbidities; their disease duration and factors predictive of rapid progression; and previous response to therapies including drug toxicity.

The potential risk versus benefit for each biological therapy needs to be individualised for each patient and their disease. Hence the prescription of biological agents requires rheumatologists' experienced in the diagnosis, treatment and assessment of RA, JIA, AS and PsA and able to use the validated quantitative response measures for disease activity and functional disability for the treatment response or to follow up each patient over time. (See Appendices)

TNF INHIBITORS

Four cytokine TNF inhibitors are available for prescription by Australian rheumatologists.

They are cost effective from a societal perspective.

They differ in protein source, mechanism of action and pharmacokinetics.

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 3.5 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 monoclonal antibody which binds to TNF- α and blocks interaction with the p55 and p75 cell surface TNF receptors. The half life is 14 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 10 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).
4. Golimumab is a human antibody given as a subcutaneous 50mg injection on the same date each month for RA, AS, and PsA.

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, etanercept and golimumab are all 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 goal) and improved radiological outcomes. Leflunomide (versus MTX) in combination with a TNF inhibitor is slightly less effective and hence may be a useful alternative in the MTX intolerant RA patient.

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 using 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. ACR 20 discriminates between acute and placebo in clinical trials but may not be clinically relevant. Modern rheumatologists with availability to several biological therapies would aim for the meaningful ACR 50 or remission goal of ACR 70 improvement and / or DAS28 < 2.6 with perhaps annual radiology and patient orientated measures annually especially in early RA. Most professional associations currently advocate not to use the ACR in day to day clinical practice.

Treatment failure including loss of response or adverse effects is observed in one-third of patients on TNF inhibitors for RA. Options to provide additional response include adding in or increasing dosage of conventional DMARDs, switching to a second TNF inhibitor, or switching to another molecular target biological agent. The optimal next decision in the treatment algorithm for a TNF-inadequate responder is not yet determined.

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.

Both infliximab and adalimumab versus etanercept are efficacious in patients with associated active inflammatory bowel disease and uveitis. AS patients can be switched between TNF inhibitors but flares usually occur with cessation despite prolonged good effect with their use over time.

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 (joints, dactylitis, enthesitis, spine and skin) and patient quality of life outcomes including work disability and radiographic inhibition 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 and are often normal range in active severe disease.

RCT data to support conventional DMARDs (sulfasalazine, methotrexate, cyclosporin, leflunomide) as first line therapy for PsA remain limited whereas RCTs with the four available TNF inhibitors all show significant responses. Efficacy has been demonstrated both with monotherapy and with background MTX.

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. Sulfasalazine has a weak DMARD role in PsA. -+

RESPONSE

1. 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, HAQ (or SF 36) or acute phase reactants (ESR or CRP). Some patients will continue to improve to week 24.

POTENTIAL ADVERSE EVENTS

1. Infections

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 case history risk assessment, chest x-ray within last three months and either two step TST skin test or QuantiFERON TB Gold blood test (Interferon Gamma Release Assay). If screening, yields positivity i.e., latent TB is possible, TB prophylaxis is recommended (isoniazid 5mg/kg/d, <300mg/d with pyridoxine 25mg/d for 6-9 months OR rifampicin 10mg/kg/d, <600mg/d for 4 months). There is general consensus for latent TB the 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 in this situation treatment should involve the local TB expert. (See Screening for LTBI Guidelines www.rheumatology.org.au)

Other infections. TNF inhibitors should not be started (or should be discontinued until treatment completed) when serious bacterial infections occur which require intravenous antibiotics and hospitalisation especially skin and soft tissue infections or abscess, septic arthritis, infected prosthesis, osteomyelitis and systemic fungal or other opportunistic infections especially non tuberculosis mycobacteria, listeriosis, coccidiomycosis or histoplasmosis.

Severe bronchiectasis especially if corticosteroid dependent may also be a contraindication for TNF inhibitor use.

Viral hepatitis infection. Patients should be screened and if Hep BsAg positive should be referred to the local liver expert and receive probably six months appropriate anti viral treatment first and continued at least six months if TNF inhibitor is still then given. Although hepatitis C appears less of a potential liver failure problem discussion with the local liver expert if TNF inhibitor commencement is being considered is suggested.

2. Malignancy. Patients should be fully aware of risk / benefit aspects and formal consent is best documented in those with background of malignancy. Lymphomas (especially non-Hodgkin's) are increased 2-5 fold in RA and associated with high disease activity. A similar risk is seen in patients using TNF inhibitors. There is conflicting data whether there is increased risk of solid malignancies and non-melanotic skin cancer. 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, treated and hopefully cured.

3. Neurological Syndromes, eg., Multiple Sclerosis, Optic Neuritis, Guillaine-Barre syndrome 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.

4. 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. Golimumab use with its citric acid free formulation reports less frequent injection site reactions.

5. Pregnancy. Most women are advised to stop prior to and during pregnancy as insufficient data is unavailable on long term foetal safety. Many women have now continued until conception.

6. Severe Congestive Heart Failure. Has been associated with some morbidity in higher dose infliximab use but in general TNF inhibitors do not increase the risk of worsening heart failure. The risk of myocardial infarct in RA patients has been shown to be reduced in those who respond to TNF inhibitors in six months. The effect on lipids is still controversial.

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. Pancytopenia, Aplastic Anaemia. Requires cessation although rarely reported and usually in context of underlying disease and / or concomitant drugs.

9. Liver Transaminase elevation. Can occur with all TNF inhibitors and again concomitant drugs, alcohol use and other conditions can confuse the picture. Rare reports of cholestatic, autoimmune or fulminant hepatitis have been described.

10. Eczema and Psoriatic skin lesions for the first time have been reported in patients with RA and AS using TNF inhibitors.

Vaccinations

There is a small decrease in the prevalence of adequate protection especially for vaccines given in combination with methotrexate. Ideally vaccination should be given before starting treatment (eg influenza, polysaccharide Pneumovax, Hep B) and then during as appropriate when indicated. Live attenuated vaccines (eg., BCG, yellow fever, herpes zoster and oral polio) are not recommended.

Surgical Procedures

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

Laboratory monitoring

Laboratory monitoring helps determine effectiveness of therapy often combined with a validated response measure 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 re-exposure to TB is occurring.

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

HIV screening should be considered in at risk patients.

ANA, DNA, RF, anti-CCP initially pre biologic. These maybe repeated if appropriate (eg ANA, DNA if development of clinical SLE symptoms).

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 and crypyrin associated periodic syndromes including, neonatal onset multi system inflammatory disease (NOMID) Muckle-Wells syndrome and familial cold autoinflammatory syndrome. Anakinra is less effective than TNF inhibitors in RA.

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 bacterial infections are increased in RA patients 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 cell targeted chimeric monoclonal 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. More effective and durable ACR responses are seen in RF/anti-CCP positive patients in TNF or DMARD non-responders.

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 a pre-medication of IV 100mg methylprednisolone, oral antihistamine and paracetamol approximately 30 mins pre-infusion. Combination with ongoing Methotrexate is recommended. 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 other TNF inhibitors, abatacept or tocilizumab. It should not be give 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 who 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

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).

REPEAT TREATMENT

Repeat treatment using the same dosing is recommended from 24 weeks following the first infusion or can be 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. There is conflicting data however on the efficacy of retreatment of initial non-responders.

POTENTIAL ADVERSE EVENTS

1. **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 general however 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. Screening is thus recommended. Use with hepatitis C is probably safe but hepatitis B and HIV infection would require consultation with the local relevant expert. Currently there does not appear to be an increase in incidents of serious infections with increasing repeat treatments. Of interest there was no increase in serious infections in one cohort who received another biological therapy after ritixumab versus those receiving rituximab before a biological agent.

2. **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.
3. **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.
4. **Neurological Syndromes.** Demyelinating syndromes are not contraindications to rituximab use. Progressive multifocal leukoencephalopathy (PML) a rare virus disease of the brain has been reported in SLE and a few RA patients given rituximab.
5. **Autoimmune-Like Syndromes** are not reported.
6. **Pregnancy.** Advise women to stop prior to and during pregnancy as insufficient data available on long term safety.
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.
8. **Skin reactions including severe psoriasis** cases have also been reported.

Laboratory monitoring is similar to TNF inhibitor use. Initial immunoglobulin levels, RF, anti-CCP and B cell levels may be done. In routine clinical practice B cell levels have not proven useful. Timing of treatment should be based on disease activity rather than repletion of peripheral B cell levels.

Although decreased levels of immunoglobulin (Ig) M, A, G may occasionally be observed with rituximab use, no statistical increase in serious infections have been reported in patients with reduced IgM levels after rituximab to date.

Vaccination advice is similar to TNF inhibitor use.

ABATACEPT

Abatacept is a cell targeted therapy selectively modulating 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. It will be rare in clinical practice that circumstances necessitate use of abatacept in DMARD-naive patients.

RESPONSE

Lack of response assessed at 12-16 weeks as per TNF inhibitors and rituximab. Patients however continue to improve for up to 12 months from commencement of treatment.

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 but does not increase over time. Similar measures should be applied as per TNF inhibitors. Incidents of intracellular infections are comparatively low. RA patients with COPD had more infective adverse events with abatacept versus placebo use in initial trials hence COPD patients should be monitored for worsening of their respiratory status.

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 but not in registers. Patients should be encouraged to stop smoking and have an annual skin check.

3. Infusion reactions included headache and dizziness but there were no significant problems and hence current availability of giving abatacept outside infusion centres after initial five infusions.

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

5. Autoimmune-Like Syndromes are not reported.

Vaccination advice is similar to TNF inhibitor use.

TOCILIZUMAB

Tocilizumab, (TCZ), is a recombinant humanized monoclonal antibody that binds to both soluble and membrane-bound IL-6 receptors. IL-6 stimulates hepatocyte production of acute phase proteins and IL-6 overproduction results in bone resorption via osteoclast activation.

The half life of tocilizumab is concentration-dependent and at steady state it is 8-14 days. It is given by intravenous infusion over an hour at 8mg/kg every 4 weeks for RA.

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. May be used in combination with methotrexate unless limited by serious toxicity or intolerance or with other DMARDs

RESPONSE

Lack of response assessed at 12-16 weeks as per TNF inhibitors and rituximab. (See RA TNF inhibitor section).

ADVERSE EFFECTS

- 1. Infections.** There is a slightly raised rate of infections with TCZ use, as with other biologics. Treatment with TCZ is contraindicated in patients with active infections. IL-6 is a major inducer of the inflammatory response against infection, thus TCZ could mask signs of infection such as fever, general malaise and elevation of CRP and ESR, consequently making the early diagnosis of infection more difficult.
In clinical trials, TB and hepatitis screening was done with exclusion of patients who tested positive. The risk of TB and effect of TCZ on hepatitis B/C viral loads are therefore unknown. All patients should be screened for latent TB, Hepatitis B/C and HIV as per the TNF inhibitor protocol.
- 2. Gastrointestinal.** Events of diverticular perforation as complications of diverticulitis have been reported. Although this adverse event is rare, TCZ should be used with caution in patients with previous history of intestinal ulceration or diverticulitis and on corticosteroids.
- 3. Malignancy.** To date the risk of malignancy is similar to that expected in the RA population. Patients should be encouraged to stop smoking and have an annual skin check.
- 4. Liver transaminase elevation.** Transient hepatic transaminase and indirect bilirubin elevations have been commonly observed in clinical trials. Combination therapy with methotrexate generally resulted in an increased incidence of AST and ALT elevation. Caution should be exercised when considering treatment of patients with active hepatic disease. Drug dosage should be reduced, interrupted or discontinued in patients with liver enzyme abnormalities, (eg. ALT or AST > 2 x ULN).
- 5. Haematological parameters.** Transient dose-dependent neutropaenia and thrombocytopenia have been reported in clinical trials. Most occurred within 8 weeks of initiation of treatment. No associations were observed between reduced counts, incidence of infection or bleeding events.
- 6. Lipid levels.** Moderate, reversible elevation in lipid parameters including total cholesterol, LDL, HDL and triglycerides has been reported. In the majority of patients with elevated lipid parameters, there was no increase in atherogenic indices and elevations responded to treatment with lipid-lowering drugs. The long-term implications of these observations are not clear at this time.
- 7. Drug interactions.** Drugs metabolized via the CYP450 enzymes (eg. warfarin and cyclosporine), should be monitored as doses may need to be adjusted to maintain therapeutic effect.
- 8. Infusion reactions** included headache, dizziness, skin reactions and episodes of hypertension during the infusion. These were not treatment limiting.
- 9. Pregnancy and Lactation.** Women should be advised to stop prior to and during pregnancy as there is insufficient data on long term foetal safety.
- 10. Surgery.** It is advisable to postpone surgery in patients on TCZ by at least 14 days after the last infusion, as the effect of IL-6 on wound healing remains to be clarified.
- 11. Autoimmune-Like Syndromes** are not reported to date

Vaccinations advice is similar to TNF inhibitor use.

Laboratory Monitoring

TB, Hepatitis B, C and HIV serology, ANA, DNA, RF, anti-CCP screening is similar to TNF inhibitor use.

Consider 4-8 weekly monitoring of FBC, LFTs and lipid parameters for the first 6 months of treatment, and then 3 monthly thereafter. Drug dosage should be reduced, interrupted or discontinued in patients with liver enzyme abnormalities (eg. AST or ALT >2 x ULN) and low absolute neutrophil count (<500).

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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