



## Biological disease-modifying anti-rheumatic drugs (bDMARDs) in rheumatic diseases A guide for GPs \*

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Rheumatoid Arthritis (RA), Juvenile Idiopathic Arthritis (JIA), Ankylosing Spondylitis (AS) and Psoriatic Arthritis (PsA) are common inflammatory rheumatic diseases affecting over 750,000 men, women and children in Australia. They cause persistent pain, stiffness and joint damage resulting in significant disability, loss of quality of life and employment. Treatment aims to induce clinical and radiological remission.

Methotrexate (MTX), used alone or in combination with other disease modifying antirheumatic drugs (DMARDs) may provide effective therapy. The addition of bDMARDs or cytokine modulators have revolutionised the management of these diseases and improved the lives of many patients. bDMARDs selectively block pro-inflammatory cytokines that play a critical role in the pathogenesis of inflammatory disease or act through B or T lymphocytes to decrease cytokine production.

### **bDMARDs that act as cytokine blockers** can inhibit

- Tumour Necrosis Factor (TNF) –adalimumab (ADA), certolizumab (CTZ),etanercept (ETN),golimumab (GOL) , infliximab (IFX)
- Interlukin-1 (IL-1) - anakinra (ANA) or
- Interlukin-6 (IL-6) – tocilizumab (TCZ).

### **bDMARDs that are cell-targeted** can be directed at

- T cells – abatacept (ABA) –inhibits a co-stimulatory signal required to activate T cells, or
- B-cells – rituximab (RTX)- inhibits CD20 antigen on the membrane of precursor and mature B cells

### **Rheumatologic indications for bDMARDs are**

- RA, refractory to an adequate trial of DMARDs
- Polyarticular juvenile idiopathic arthritis (JIA), refractory to one or more DMARDs
- Ankylosing spondylitis
- Psoriatic arthritis

bDMARDs have been proven to be very effective in treating severe RA, are cost effective and work faster than traditional DMARDs.

Although bDMARDs all block the biologic effects of various cytokines, there are differences in their protein source, mechanism of action, pharmacokinetics and structure see table 1.

Table 1 characteristics of PBS funded bDMARDs available in Australia for rheumatic disease

Generic name	adalimumab	certolizumab	etanercept	golimumab	infliximab	abatacept	anakinra	rituximab	tocilizumab
Accepted abbreviation	ADA	CTZ	ETN	GOL	IFX	ABA	ANA	RTX	TCZ
Trade name	Humira	Cimzia	Enbrel	Simponi	Remicade	Orencia	Kineret	MabThera	Actemra
Target	TNF	TNF	TNF receptor	TNF	TNF	T-cells (CD 80/86)	IL1 receptor	B-cells (CD20 )	IL6 receptor
Type of protein	monoclonal antibody	monoclonal antibody	fusion protein	monoclonal antibody	monoclonal antibody	monoclonal antibody	fusion protein	monoclonal antibody	monoclonal antibody
Protein source	human	human	human	human	human and mouse	human	human	human and mouse	human
Half-life	12-14 d	14 d	3.3 d	12 d	9d	13 d	6 h	21 d	8-14 d
Dose	40mg	200mg eow or 400mg each 4 <sup>th</sup> week	50 mg once or 25mg twice a week	50mg	3-5mg/kg	10mg/kg	100mg	1000mg	8mg/kg
Administration	SC	SC	SC	SC	IV	IV	SC	IV	IV
Frequency	2 weeks	2-4 weeks	1-2 times a week	monthly	Baseline then infusions at 6–8 weekly intervals	4 weekly	daily	Day 1 & 15, then at 6 monthly intervals	4 weekly
Onset of benefit (weeks)	2-4	1-4	2-4	8	2-4	4-8	4-12	12	8
PBS MTX requirement		√ Unless contraindicated or not tolerated		√ for RA	√ for RA	√	√	√	
Indications	AS, JIA, RA, PsA	RA	AS, JIA, RA, PsA	AS, RA, PsA	AS, RA, PsA	RA	RA	RA	RA

## **POINTS TO CONSIDER WITH bDMARDS**

These medications are generally well tolerated but the existence of any contraindications to their use needs to be considered before the commencement.

**Pre-bDMARD screening:** - All patients are screened for latent tuberculosis infection (LTBI) with Mantoux test +/-QuantiferON-TB Gold assay and CXR before starting therapy. Active or LTBI must be treated with a standard anti-TB regimen. There is general consensus that bDMARD can be commenced concurrently after 4-8 weeks of starting anti-TB regimen. (See Screening for LTBI Guidelines [www.rheumatology.org.au](http://www.rheumatology.org.au))

**Vaccinations:** - Patients being treated with bDMARDs, particularly if in combination with MTX have a small reduction in response to vaccinations. Studies in children have demonstrated maintenance of immunity and good response to immunisation. Vaccinations should be given before starting treatment (e.g. influenza/H1N1, polysaccharide Pneumovax, Hep B) and then during as appropriately indicated. Live attenuated vaccines (e.g. rubella (MMR), BCG, yellow fever, herpes zoster and oral polio) are not recommended.

**Surgical Procedures:** - There currently is no evidenced based consensus on how bDMARDs should be managed in the context of elective surgery, but the increase risk of infection in RA patients continuing bDMARDs during joint replacement has been reported. Current recommendations include withholding treatment with ETN for 2-4 weeks and other bDMARD for 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.

## **POTENTIAL ADVERSE EVENTS**

**Infections:** - There is an increased risk of severe infections with bDMARDs. Patients should be instructed on ways to differentiate simple viral illnesses/minor infections from those with the potential to cause serious harm. If patients have a serious infection that requires IV antibiotics and hospitalisation the bDMARDs should be discontinued and/or not be commenced. In such cases the treating rheumatologist needs to be informed. Severe bronchiectasis, especially if corticosteroid dependent, may influence choice of bDMARD. Hep C is not a contraindication to the use of bDMARDs. Hep BsAg positive patients should receive appropriate anti viral treatment prophylactically with continuation as long the bDMARD is given.

**Injection site / infusion reactions:** - Mild to moderate injection site (local erythema, pruritus and swelling which usually subsides within 24 hours) and infusion (fever, chills, nausea) reactions are common. They can be treated with antihistamine, corticosteroids and slowing infusion rate. Cessation of drug is rarely required.

**Malignancy:** - Lymphoma is 2-5 times more common in patients with severe active RA than the general population. There is conflicting data whether the risk of malignancy is changed with bDMARD treatment. Registries suggest a previous history of malignancy is associated with an increased risk. At present an interval of at least 5 years is suggested between cure of a cancer and starting bDMARDs. Patients should be encouraged to stop smoking and, until more definitive evidence is available, undergo regular skin checks. There is a lack of data to guide decisions about restarting a bDMARD after successful treatment of a cancer. Patients should be fully aware of risk/benefit aspects and decisions should be made on an individual basis taking into account all factors including quality of life.

**Neurological Syndromes:** - TNFi should not be started or should be stopped if demyelinating syndromes, such as multiple sclerosis, optic neuritis or Guillain-Barre syndrome, occur. Progressive multifocal leukoencephalopathy (PML), a rare viral disease of the brain is found more commonly in patients with systemic lupus erythematosus (SLE) and RA than in the general population. This may be increased further in patients with SLE or RA who are given RTX.

**Severe Congestive Heart Failure:** - There has been conflicting data as to whether TNFi may exacerbate CHF, particularly in elderly patients. The risk of myocardial infarct in RA patients has been shown to be reduced in those who respond to TNFi in six months. Screening for cardiac risk factors and effective treatment of both rheumatic and cardiac disease are essential.

**Autoimmune-Like Syndromes:** - There is increased incidence of ANAs +/-dsDNAs after TNFi. The development of clinical drug-induced lupus, vasculitis and antiphospholipid syndromes is rare but requires TNFi 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 TNFi.

**Haematological abnormalities:** - These are rare. Transient dose-dependent neutropaenia and thrombocytopaenia have been reported with TCZ. Very rarely late-onset neutropaenia, delayed pancytopaenia or aplastic anaemia has been recorded with other bDMARDs.

**Liver function elevations:** - Elevations in transaminase+/- indirect bilirubin elevations have been observed. Regular monitoring is required. Concomitant medications, alcohol use and other conditions can confuse the picture.

**Skin reactions:** - A variety of skin conditions including severe psoriasis cases have been reported in patients with RA and AS using bDMARDs.

**Gastrointestinal:** - Complications of diverticulitis, including intestinal perforation, have been reported with TCZ.

**Lipid levels:** - moderate, reversible elevations in lipid parameters have been reported with TCZ. In the majority of patients there was no increase in atherogenic indices and elevations responded to treatment with lipid-lowering drugs.

**Drug interactions:** - Drugs metabolised via the CYP450 enzymes (e.g. warfarin and CYA), should be monitored as doses may need to be adjusted to maintain therapeutic effect with TCZ.

**COPD:** - trials showed ABA can exacerbate COPD. Respiratory status should be monitored.

#### **OTHER POINTS FOR CONSIDERATION.**

**Pregnancy:** - To date registries have not identified any signals to suggest increased teratogenicity. However due to small numbers and insufficient data on long term foetal safety, recommendations have been to cease treatment before a pregnancy is planned, at a time dependent on the specific bDMARD. Discontinuation is recommended if unexpected pregnancy occurs. There are case reports of women continuing TNFi both until conception and during pregnancy without apparent adverse effects.

**Laboratory monitoring:** - Combined with a validated response measure the ESR/CRP are required to determine effectiveness of therapy. Generally three monthly ESR, CRP, FBC, electrolytes, creatinine, and LFTs are recommended but frequency may be influenced by concomitant DMARD use.

**TNFi should be not be used with other bDMARDs. Patients may be switched from one TNFi to another at the time of the next dose. TNFi should not be given within 8 weeks of treatment with ABA, RTX or TCZ.**

#### **\* DISCLAIMER**

*These recommendations are written to inform Australian GPs about bDMARD use in rheumatic diseases. They were prepared from 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 as new data and new agents become available.*

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