Australian Rheumatology Association

GUIDELINES ON BIOLOGICAL AGENTS AND SMALL MOLECULE MEDICATIONS FOR THE TREATMENT OF RHEUMATIC DISEASES*

*** DISCLAIMER**

These recommendations are written to provide information to Australian health professionals about biological agents (bDMARDS) in rheumatic diseases. They are updated regularly as new data and 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 and reflect worldwide recommendations. They are non-mandatory, for educational purposes only and subject to continuing change. They differ from the current Medicare Australia requirements for PBS subsidised prescription of bDMARDs.

INTRODUCTION

Rheumatoid Arthritis (RA), Juvenile Idiopathic Arthritis (JIA), Ankylosing Spondylitis (AS), Non-Radiographic Spondyloarthritis (NR-SpA) 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 remission with treatment to target strategies or tight control of disease activity. Conventional disease-modifying anti-rheumatic drugs (DMARDs), primarily methotrexate (MTX), used alone or in combination may provide adequate therapy for some people with severe JIA, PsA and up to one third of those with early RA, but are regarded as ineffective in people with AS.

Biological agents (biologics or bDMARDS) are molecules that are manufactured via biological processes to produce large antibody molecules. They are poorly absorbed in the gut and require injection either subcutaneously or intravenously. They generally also require refrigeration. They are usually antibodies that may be cell-targeted or selectively block cytokines found in excessive amounts in people with these conditions. Some biologics (rituximab and tocilizumab) have also been approved for different types of vasculitis. Small molecule medications (such as the JAK inhibitors tofacitinib, baricitinib and upadacitinib) on the other hand, are easily absorbed and hence can be administered as tablets. These are kinases that work intracellularly. These drugs have potential toxicities similar to bDMARDs and have similar costs. For this reason, the PBS requires the same criteria and application process and they are discussed alongside bDMARDs in this article.

Biological agents (bDMARDs) and small molecule medications have revolutionised the management of these diseases and improved the lives of many patients including those with an inadequate response to MTX. Their use should take into account cost, route of administration, availability, patient characteristics and co-morbidities, disease duration, factors predictive of rapid progression and previous response to therapies including drug toxicity.

Biosimilars are also bDMARDs. These are similar molecules to the originator bDMARD but manufacturing processes may differ slightly. In Australia, in order to be approved for use, the biosimilars have been compared to the originator bDMARD to ensure similar efficacy and safety. At this time, we are not sure if issues will arise from switching between biosimilars and the originator either from differences in outcomes or immunogenicity. In Australia, A-flagging does allow

pharmacists to substitute the biosimilar brands and originator brands, for further information on the introduction of biosimilars for the Treatment of Rheumatic Disease can be found here.

The potential risk versus benefit for each bDMARD needs to be considered for each patient and their disease. The bDMARDs and small molecules are highly restricted due to cost and safety concerns and patients must reach certain criteria in terms of their disease severity and previous DMARD failures to qualify. The treating rheumatologist applies to the PBS for the patient to receive an approved prescription every 4 months (for initial prescriptions) to 6 months (for continuations).

DMARDs and bDMARDs are frequently given together but it is not recommended that more than one bDMARD or small molecule is given at a time due to infection concerns.

GENERAL RECOMMENDATIONS

Side effects to monitor for:

1. For injections/infusions - Injection site/infusion reactions – to reduce the potential risk, leave the subcutaneous injection out of fridge 30-60 mins prior
2. Abnormalities of LFTs, FBE, UEC, (and lipids with tocilizimab, tofacitinib, baricitinib, upadacitinib, secukinumab and ixekizumab)
3. Usual infections (nasopharyngeal, respiratory, urinary tract, soft tissue and skin): withhold biologics if needing antibiotics until infection resolves
4. Consider unusual infections, opportunistic infections and strange presentations of any infections. Note, sometimes there are no fevers and sometimes normal inflammatory markers (TB, Listeria, Salmonella, Herpes viruses)
5. Diverticulitis more common with tocilizumab and tofacitinib, baricitinib and upadacitinib, with cases of diverticular perforation reported.
6. Cardiac failure (TNF inhibitors)
7. Autoimmune syndromes or demyelination (TNF inhibitors): SLE, MS, Optic neuritis, GBS (although rare)
8. Thrombotic risk may be associated with JAK inhibitors (tofacitinib, baricitinib, upadacitinib)
9. Monitor for higher rate of lymphoma in rheumatology patients in general
10. Skin cancers: patients should have an annual dermatology review (skin check)
11. Age specific cancer screening should be routinely performed (PAP tests, mammograms, etc) especially in patients on immunosuppression

Recommended Vaccines:

1. Fluvax annually, Pneumococcal 23 & 13 (5 yearly)
2. If at risk: Hepatitis B / Hepatitis A & HPV
3. Avoid live vaccines in patients on biologics – Avoid Zostervax vaccine unless discussed with rheumatologist, consider vaccination prior to immune suppressing treatment
4. Tetanus Toxin is regarded as safe but need to use Tetanus Immunoglobulin if <6 months since last rituximab dose
5. Babies of mothers who stayed on biologics during pregnancy must avoid all live vaccines for the first 6 months of life (eg. Rotavirus is a live vaccine given at 2 and 4 months)

Pregnancy/Breastfeeding

Avoid exposure to bDMARDs if possible, but some can be continued in certain situations. Inform rheumatologist as soon as patient is planning to conceive. Use of TNF inhibitors may be considered in the first 2 trimesters and Certolizumab may be preferred during pregnancy due to minimal placental transfer even in 3rd trimester. Other agents have insufficient data to make recommendations. Please see Pregnancy Guidelines.

Surgery
If practical stop bDMARD prior to surgery, timing will depend on the particular biological medication. Generally, one dose cycle can be withheld for subcutaneous/intravenous bDMARDs and 1 week of treatment withheld prior to surgery for small molecule medications. There is limited evidence to guide this recommendation and the decision must take into account the severity of the disease and risk of disease flare along with the risk of infection. Recommence when wound healed provided no infective complications.

Travel
Patients need to plan ahead (vaccines, supplies of medication, storage of medication, letters for customs, travel insurance all need to be considered).

Diet
A diet similar to that recommended for pregnant women has been suggested (ie. avoid raw, uncooked food, soft cheeses etc) for patients taking bDMARDs to 'to prevent rare but occasionally severe cases of Listeria and salmonella.

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 and where appropriate lipid studies.
- Chest x-ray (pre biologic and post if respiratory symptoms or LTBI follow up, or smoker). Refer to Screening for Latent Tuberculosis Infection (LTBI) and its management in Inflammatory arthritis patients
- 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, dsDNA, RF, anti-CCP initially pre biologic. These maybe repeated if appropriate (e.g. ANA, dsDNA if development of clinical SLE symptoms).

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Therapeutics Committee
Australian Rheumatology Association
145 Macquarie Street, SYDNEY NSW 2000
Tel: 02 9252 2356 email: admin@rheumatology.org.au

Table 1. **BIOLOGICAL DMARDS AND SMALL MOLECULES ON PBS FOR RHEUMATOLOGY INDICATIONS IN AUSTRALIA**

bDMARD	Mode of Action	Indications	Presentation	Dose for Rheum indications	Potential Side-effects	Brands	Comments
TNF Inhibitors	Inhibit TNF cytokine effects				Class effects of TNF inhibitors: include: risk of infections, TB reactivation/infection, viral reactivation, injection site reactions, allergic reactions, paradoxical psoriasis, CHF, SLE, MS, GBS, ON		
Adalimumab	mAb	RA, PsA, NR-SpA, AS, JIA, Ps0, UC, Crohn, Uveitis, hidradenitis suppurativa	20 and 40mg syringe or pen for subcutaneous injection	Generally 40mg fortnightly SCIthough higher doses are sometimes used. In JIA if <30kg 20mg fortnightly		Humira	
Certolizumab	mAb - pegylated Fab fragment	RA, PsA, AS, NR-SpA	200mg syringe or pen	200mg fortnightly or 400mg every 4 weeks after loading 400mg every 2 weeks for 3 doses		Cimzia	Preferred TNF inhibitor in pregnancy as no Fc fragment and minimal placental transfer
Etanercept	TNF receptor blocker	RA, PsA, AS, JIA, Ps0	25mg and 50mg syringe or pen for subcutaneous injection	25mg twice weekly (304 days aoart) or 50mg weekly SCI: In JIA (2-17yo) 0.4mg/kg twice a week up to max 25mg or 0.8mg/kg weekly up to 50mg/week		Enbrel, Brenzys (Biosimilar)	Lower risk of TB reactivation than mAb but slight risk
Golimumab	mAb	RA, PsA, AS, NR-SpA, UC	50mg syringe or pen, (100mg pen UC only) for subcutaneous injection	50mg every 4 weeks		Simponi	In RA: PBS require combination with weekly methotrexate
Infliximab	mAb - chimeric mouse protein	RA, PsA, AS, Ps0, Crohn, UC	infusion, 100mg vials for intravenous infusion	RA:3mg/kg every 8 wks after loading 3mg/kg at wks 0,2 and 6; PsA 5mg/kg, every 8 wks after loading 3mg/kg at wks 0,2 and 6; AS: 5mg/kg every 6 wks after loading 5mg/kg at wks 0,2,6 wks		Remicade, Biosimilars (Inflectra, Renflexis)	Potential for reaction due to mouse protein, administered with antihistamines and glucocorticoids; In RA: PBS requires combination with weekly methotrexate

Legend: TNF: tumour necrosis factor, TB: Tuberculosis, CHF: Congestive Heart Failure, SLE: Systemic lupus erythrematosis, MS: Multiple sclerosis, GBS: guillain barre syndrome, ON: Optic Neuritis, mAb: Monoclonal antibody, RA: Rheumatoid arthritis, PsA: Psoriatic arthritis, AS: Ankylosing spondylitis, JIA: Juvenile inflammatory arthritis, Ps0: Psoriasis, UC:Ulcerative colitis, SCI: Subcutaneous injection, NR-SpA: Non-Radiographic spondyloarthritis, APC: Antigen presenting cell, wt: weight, IV: intravenous, MPA: Microscopic polyangiitis, GPA: granulomatous polyangiitis, NHL: Non Hodgkins lymphoma, CLL: Chronic Lymphocytic leukemia,, GCA: Giant cell arteritis, IL: interleukin, LFT: Liver function test, q4w: every 4 weeks, q3w: every 3 weeks, q2w: every 2 weeks, BD: twice daily, PO: per oral, OD: oral daily, NR-SpA: Non-Radiographic Spondyloarthritis

bDMARD	Mode of Action	Indications	Presentation	Dose for Rheum indications	Potential Side-effects	Precautions	Brands	Comments
Other bDMARDs								
Abatacept	mAb binding CD80 and CD86 on APC cells inhibiting costimulation of T cells	RA	125mg syringe/pen or 250mg vial for infusion	125mg weekly SCI or wt based dosing IV every 4 weeks after initial loading at wks 0, 2,& 4 wks (<60kg 500mg, 60-100kg 750mg, >100kg 1000mg)	infections, TB reactivation/infection, viral reactivation, injection site reactions		Orencia	PBS requires combination with weekly methotrexate
Rituximab	mAb - mouse protein to CD20 B cells	RA, Vasculitis (MPA, GPA), NHL, CLL	500mg , 100mg, 1.4g vials for IV	RA: 1g IV 2 weeks apart repeated at minimum every 6 months; GPA: 375mg/m2BSA weekly IV for 4 doses	infections, TB reactivation/infections, viral reactivation including hepatitis B reactivation, infusion reactions, neutropenia, rare risk of PML, reduced IgG, late onset neutropenia	Requires premed of antihistamines and glucocorticoids to avoid reactions due to mouse protein	Mabthera, Mabthera Sc, Biosimilar (Riximiyo)	For RA: PBS requires combination with weekly methotrexate
Tocilizumab	IL-6 inhibitor	RA, GCA, JIA	162mg syringe or pen , 80mg,200mg. 400mg vials for infusion	162mg weekly SCI (RA or GCA) or 8mg/kg IV q4w (RA only); pJIA <30kg 10mg/kg q4w or 162mg q3w, =/> 30kg 8mg/kg q4w or 162mg q2w; sJIA <30kg 12mg/kg IV q4w, =/>30kg 8mg/kg q4w IV.	Infections, TB reactivation/infection, viral reactivation, neutropenia, abnormal LFTs, increased lipids, risk of bowel perforation with diverticulitis	Avoid in diverticulitis, Potential drug interactions with P450 CYP3A4 (rifampicin, ketaconazole, fluconazole etc), gastric perforation has been reported	Actemra	
Ustekinumab	mAb to IL-23 and IL12	PsA, Ps0, Crohn	45mg or 130mg vial	For PsA: 45mg at weeks 0,4 then every 12 weeks SCI	infections (but very low rate)		Stelara	
IL-17 Inhibitors					Class effect: Infections - usual and slightly higher rate topical fungal infections, neutropenia, abnormal LFTs, increased lipids	Note: no effect on inflammatory bowel disease and may exacerbate		
Secukinumab	mAb IL-17A	PsA Ps0, AS	150mg pen or syringe	For PsA: 150-300mg at weeks 0,1,2,3,4,5 then every calendar month SCI. For AS - maximum PBS allowed is 150mg			Cosentyx	

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bDMARD	Mode of Action	Indications	Presentation	Dose for Rheum indications	Potential Side-effects	Precautions	Brands	Comments
Small Molecules								
JAK inhibitors					Class effects: Infections (usual, TB reactivation/infection, higher risk of Herpes Zoster and other viral reactivation), cytopenias, abnormal LFTs, increased lipids			
Tofacitinib	Blocks predominantly JAK 1 & 3	RA, PsA, Ps0	5mg tab	RA & PsA: 5mg BD	Thromboses reported with higher doses (10mg BD)	Potential drug interactions with P450 CYP3A4 (rifampicin, ketaconazole, fluconazole etc), gastric perforation has been reported	Xeljanz	dose reduce in renal impairment
Baricitinib	Blocks predominantly JAK 1 & 2	RA	2mg and 4mg tab	RA: 4mg od	Possible thrombotic risk, thrombocytosis		Olumiant	
Upadacitinib	Blocks predominantly JAK 1	RA	15mg tab	RA: 15mg od	Possible thrombotic risk		Rinvoq	

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