An Australian Living Guideline for the Management of Juvenile Idiopathic Arthritis

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Contact

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1. Management of JIA with DMARDs

Juvenile idiopathic arthritis (JIA) is the most common chronic rheumatic disease in childhood. JIA is an umbrella term for a heterogeneous group of disorders that manifest as early onset arthritis *[19]*.

The cause of JIA is not completely understood but is probably due to a combination of genetic and environmental factors. It affects approximately 1-4 per 1,000 children under the age of 16. Girls are more commonly affected than boys in an overall ratio of approximately 3:2 but the ratio varies significantly between JIA subtypes *[27]*. It is a heterogeneous condition with varied long-term outcomes.

The spectrum of available treatments for JIA is expanding. Commonly used treatments include non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, conventional synthetic disease modifying anti-rheumatic drugs (csDMARDs), biologic DMARDs (bDMARDs) and targeted synthetic DMARDS (tsDMARDs). With contemporary treatments, the aim of treatment is to achieve disease remission for most patients *[21]*.

JIA typically manifests with arthritis, although extra-articular symptoms such as fever, constitutional symptoms and ocular inflammation can also occur.

1.1 Benefits and harms of using bDMARD or tsDMARDs in patients with JIA associated uveitis who have not responded to methotrexate

Uveitis is the most common extra-articular manifestation of JIA, affecting 10-20% of patients and is a major source of morbidity *[22]*. JIA-associated uveitis is often asymptomatic and active uveitis screening is paramount so that it can be detected and treated. If not treated effectively, there is a high risk of uveitis leading to irreversible ocular damage and visual impairment.

Treatment of JIA-associated uveitis must be tailored to an individual patient depending on their disease severity, complications, response to prior treatments and comorbidities. Corticosteroids (topical or systemic) are often used as first line treatment however their use is limited by dose dependent complications such as cataract and glaucoma. Methotrexate is well established as the first line DMARD for most patients with uveitis and is effective in approximately three quarters of patients *[24]*.

A range of treatments have been used for patients with JIA associated uveitis that is refractory to methotrexate treatment although the evidence to support such treatments is largely based on low grades of evidence such as case series. Indirect evidence suggests improved uveitis outcomes since the introduction of bDMARDs *[8]*.

Executive summary

In children and young people with JIA-associated uveitis who have not responded to methotrexate, b/tsDMARDs:

- may increase the likelihood of achieving treatment response
- may decrease the likelihood of a uveitis flare or treatment failure
- may increase the likelihood of weaning topical steroid drops to two or less per day
- may have little or no effect on the number of eyes with improvement in anterior chamber (AC) cell count
- may have little or no effect on the number of serious adverse events

We are uncertain of the effect of b/tsDMARDs on the development of new structural ocular comorbidities or visual acuity due to very low certainty of evidence.

Data on patient global assessment of disease activity and childhood health assessment questionnaire (CHAQ) were not able to be extracted from the available trials.

We did not identify any included studies examining tsDMARDs or non-TNF-α inhibitor bDMARDs.

Abbreviations used in this recommendation:

- AC - anterior chamber
- ANZMUSC - Australia & New Zealand musculoskeletal clinical trials network
- CHAQ - childhood health assessment questionnaire
- DMARD - disease modifying anti-rheumatic drug
- bDMARDs - biological DMARD, including TNF-α inhibitors (infliximab, etanercept, adalimumab, certolizumab, golimumab), interleukin-6 inhibitors (tocilizumab), T-cell costimulatory signal inhibitors (abatacept), B-cell inhibitors (rituximab)

- tsDMARDs - targeted synthetic DMARDs, including Janus Kinase inhibitors (eg tofacitinib, baricitinib)
- b/tsDMARDs - either bDMARDs or tsDMARDs
- JIA - juvenile idiopathic arthritis
- PBS - pharmaceutical benefits scheme
- RCT - randomised control trial
- SUN - standardization of uveitis nomenclature
- TNF-α - tumor necrosis factor alpha

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Publication approval and public consultation

The consortium is seeking NHMRC approval of the guideline under section 14A of the National Health and Medical Research Council Act 1992. As part of the approval process (and for the lifetime of the guidelines), public consultation is required. We welcome your feedback and suggestions. Comments can be submitted via the 'feedback' function under each recommendation in MAGICapp. For more information about how to leave feedback, please refer to Section 1 above 'How to use this Guideline'.

Conditional recommendation

In children and young people with JIA-associated uveitis who have not responded to methotrexate, b/tsDMARDs should be considered. Adalimumab is recommended over other b/tsDMARDs. Etanercept is not recommended.

Practical Info

- When considering b/tsDMARD for children and young people with JIA-associated uveitis who have not responded to methotrexate:
  - Adalimumab is recommended over other b/tsDMARDs
  - Anti-TNF-α fusion proteins (etanercept) should not be used
  - Other anti-TNF-α monoclonal antibodies (including infliximab), non-TNF-α inhibitor bDMARDs and tsDMARDs can be considered although randomised evidence supporting efficacy or safety is lacking
- Any decision regarding the use of b/tsDMARDs should be made within a shared decision-making framework following a clear discussion of potential benefits and harms, tailored to the individual's circumstances (including comorbidities and concomitant medications).
- b/tsDMARD treatment should be performed under the supervision of paediatric rheumatology and ophthalmology specialists with expertise in JIA-associated uveitis. Regular review is required to determine treatment response and medication tolerability.

Evidence To Decision

Benefits and harms

Small net benefit, or little difference between alternatives

Considering the overall benefits and harms (as summarised below), the panel concluded that there is a small to substantial benefit in recommending b/tsDMARDs in this population. Based on data from three randomised control trials (RCTs) in children and young people with JIA-associated uveitis who have not adequately responded to methotrexate, the use of b/tsDMARDs *[1][2][3]*:

- may increase the likelihood of achieving treatment response
- may decrease the likelihood of a uveitis flare or treatment failure
- may increase the likelihood of weaning topical steroid drops to two or less per day
- may have little or no effect on the number of eyes with improvement in anterior chamber (AC) cell count
- may have little or no effect on the number of serious adverse events

It is uncertain whether b/tsDMARDs have an effect on the development of new structural ocular comorbidities or visual acuity to to very low certainty of evidence.

Data on patient global assessment of disease activity and childhood health assessment questionnaire (CHAQ) were not able to be extracted from the available trials.

While the participant numbers in the included trials is limited (n=133), the overall results are consistent with observational trials. Etanercept and adalimumab are both tumour necrosis factor alpha (TNF-α) inhibitors but achieve this through different mechanisms and therefore have slightly different properties from one another *[32][33][34][35]*. TNF-α inhibitors, also known as anti-TNF-α medications, can broadly be described as either monoclonal antibodies (adalimumab, infliximab, golimumab, certolizumab) or fusion proteins (etanercept). In keeping with the findings from this review, data from JIA-associated uveitis registries and case series suggest that anti-TNF-α monoclonal antibodies have superior treatment effect on uveitis when compared to fusion proteins *[29][14][16]*. Similar findings have been noted among adults with uveitis *[30]*. For these reasons, etanercept is not generally recommended for the treatment of JIA-associated uveitis *[5][6][9][25]*.

Cohort studies looking specifically at anti-TNF-α monoclonal antibodies suggest that a significant number of patients with JIA-associated uveitis will respond favourably *[7][15][28][31]* and their use is supported in contemporary guidelines *[5][6][9][25]*.

RCTs are typically not powered to estimate differences in adverse events and may not have long enough follow-up periods to detect important long-term harms. The included trials were not able to detect a significant difference in the rate of ocular damage (measured by new structural ocular comorbidities or change in visual acuity) or serious adverse events. All three trials had pre-defined safety measures to censor patients and withdraw them from the trial in the event of a uveitis flare. After withdrawing from the trial, patients could be managed as per the treating team and were eligible to commence the investigational drug. Therefore, patients were unlikely to be exposed to prolonged periods of active inflammation and subsequent damage. This practice reflects the real world practice of treat to target strategies *[21]*. Observational trials are perhaps better at assessing for these long term complications of disease and support a positive treatment effect for bDMARDs *[8][36]*.

The side-effect profile of etanercept and adalimumab is well established through trials in other paediatric populations and post-marketing surveillance studies *[13]*. The number of serious adverse events among the RCTs included in this review were low and they did not reveal any new concerning safety signals.

Certainty of the Evidence Low

There was **low certainty evidence** for likelihood of achieving treatment response, likelihood of a uveitis flare / treatment failure, likelihood of weaning topical steroid drops to two or less per day, number of eyes with improvement in AC cell count and number of serious adverse events. There was **very low certainty evidence** for the development of new structural ocular comorbidities and visual acuity. This uncertainty was largely due to indirectness (inclusion of only two types of bDMARDs, inclusion of patients with mild disease, short follow up period) and imprecision (low number of trial participants).

It must be noted that the available RCTs are limited to only two bDMARDs (2 adalimumab RCTs, 1 etanercept RCT). Contemporary guidelines make reference to other bDMARDs for the treatment of JIA associated uveitis including other TNF-α inhibitors (infliximab, golimumab, certolizumab), interleukin-6 inhibitors (tocilizumab), T-cell costimulatory signal inhibitors (abatacept) and B-cell inhibitors (rituximab) *[5][6][9]*. Given this review was limited to only two medications, we are unsure whether these findings can be extrapolated to other bDMARDs or to tsDMARDs.

There are two ongoing trials (1 baricitinib, 1 adalimumab) with anticipated completion dates in 2022 and 2024 *[4][20]*. The results of these trials may impact the findings from this review.

The panel generally agreed with the plain language summaries although concerns were raised about the certainty of evidence. It was noted that some participants in one study (n=31) had very mild disease at baseline *[1]*. The major concern was that this could limit the applicability of this finding and potentially underestimate the treatment effect (particularly with regard to the number of affected eyes with AC cell count improvement given that this was the only trial included for this outcome).

It was also noted that the timeframe for follow up was relatively short and that RCTs are generally poorly set up to detect ocular damage (including new structural ocular comorbidities or change in visual acuity). While these are very important outcomes, it was determined that the certainty of evidence for these outcomes should be downgraded to very low.

Preference and values No substantial variability expected

A recent qualitative thematic analysis on patients with JIA-associated uveitis provides some insight into perspectives on the disease impact. Patients highlighted impacts of treatment (emotional response to treatment, medication side-effects, need for painful injections) and impacts of the disease (difficulties with seeing, risk of blindness, need for surgery) as significantly affecting their quality of life and emotional well-being *[23]*.

The panel agreed that the impacts of disease and treatments are important to consider, however most consumers would choose treatment with b/tsDMARDs.

Resources No important issues with the recommended alternative

b/tsDMARDs are a major cost to the Australian health care system. At the time of publication, the Pharmaceutical Benefits Scheme (PBS) listed price (including the approved ex-manufacturer price and all relevant dispensing fees and mark-ups) of adalimumab is $11,511.50 AUD per patient per year.

An analysis on cost effectiveness of one of the RCTs included in this review concluded that adalimumab is not cost effective when compared with methotrexate alone in the United Kingdom setting despite showing clinical efficacy *[2][12]*. It must be noted that this analysis only considered short term health care expenditure and did not consider the longer term medical, societal or economic effects of treatment. The trial design, where participants were censored on flaring and able to access the investigational medication at that point, probably limited the ability to detect meaningful short term differences in visual acuity and structural ocular complications.

The costs to society of the sequelae of under-treated uveitis must not be underestimated. Observational studies of patients with non-infectious uveitis (particularly JIA-associated uveitis) in the era of bDMARDs shows improved outcomes when

compared to historical comparison groups. Rates of visual impairment and other ocular complications appear to be considerably lower *[8]*.

While the high treatment cost was considered by the panel, it was still felt that the findings of this review support the use of b/tsDMARDs given the implications of not using them. The permanent nature of ocular damage was highlighted. It was additionally noted that generic forms of these medications ('biosimilars' in the case of bDMARDs) are expected to be available in the near future and are likely to decrease the cost. Given that bDMARDs and tsDMARDs are often currently funded through industry funded compassionate access programs, there is no direct cost to the healthcare system at present. Regardless, a majority of the panel agreed that the cost of bDMARDs/tsDMARDs favours a recommendation for their use.

Equity

Important issues, or potential issues not investigated

Equity has been considered with the PROGRESS framework (place of residence, race/ ethnicity/culture/language, occupation, gender/ sex, religion, education, socioeconomic status, and social capital) considered *[18]*.

Financial constraints, the absence of specialists to supervise the use of drugs in clinical practice and drug unavailability have all been identified as major barriers to the use of b/tsDMARDs in Australasia *[26]*.

The provision of tertiary paediatric rheumatology care in Australia is relatively constrained to major cities *[10]*. Given the complexity and expense of b/tsDMARDs, it is unlikely that they are accessible without input from a metropolitan treating unit. Patients with low health literacy and self advocacy may also have limited access to these therapies.

The panel noted that this question pertains to patients already on methotrexate, meaning that they are highly likely to already be linked in with a tertiary paediatric rheumatology and ophthalmology service, decreasing the concerns about inequity. There was an equal number of panelists voting that b/tsDMARDs probably increase or probably have no impact on inequality.

Acceptability

No important issues with the recommended alternative

bDMARDs are given parenterally (by either subcutaneous or intravenous injection), while tsDMARDs are generally orally administered. Both add to the overall treatment burden experienced by patients with JIA-associated uveitis.

Injections are consistently highlighted as a drawback by children and young people with JIA on biologic medications however many patients are able to rationalise this treatment if it leads to improved disease control or reduction in overall treatment related side-effects *[17]*. These concerns may also be partially offset by concerns about possible complications of untreated disease and implications for schooling and other activities *[23]*.

There is little evidence regarding the acceptability of b/tsDMARDs for the treatment of JIA-associated uveitis to clinicians, policymakers or other stakeholders, although the panel felt that use of these treatments in a shared decision-making framework would likely be acceptable to all stakeholders. The panel additionally noted that some modern formulations of subcutaneous bDMARDs without irritant preservatives (such as citrate) may partially alleviate concerns about painful injections. Most panellists agreed that b/tsDMARD are acceptable to all stakeholders.

Feasibility

Important issues, or potential issues not investigated

There are no bDMARDs or tsDMARDs currently listed on the Pharmaceutical Benefits Scheme (PBS) to provide subsidised access to these treatments for the indication of JIA-associated uveitis in Australia. Access is dependent on compassionate access programs through pharmaceutical companies or hospital based therapeutic groups at present. It was noted by the panel that similar healthcare systems, including England and New Zealand, support programs that provide government funded access to bDMARDs including adalimumab for JIA-associated uveitis when certain clinical criteria are met.

The majority of panel members felt that it is probably feasible to recommend this intervention.

Rationale

The panel considered evidence from RCTs that included patients with JIA-associated uveitis that has not adequately responded to methotrexate, treated with b/tdDMARDs.

Conclusions were limited by low participant numbers, relatively short follow up periods, heterogeneity with regard to outcome measures and a limited selection of bDMARDs assessed. The panel spent some time discussing outcome measures. Ocular damage (new structural ocular comorbidities or change in visual acuity) was highlighted as perhaps the most important long term outcome but one that is very difficult to assess in a randomised control trial environment. Two outcomes assessing ocular damage were deemed as being of very low certainty while the other included outcome measures were assessed as low certainty.

The panel agreed that not all bDMARDs and tsDMARDs are equal. All of the data considered by the panel were from patients treated with TNF-α inhibitors. The etanercept trial, albeit limited to 12 participants, did not show any apparent beneficial treatment effect while the two adalimumab trials suggested a positive treatment response. These findings are supported by observational studies and there are also physiological reasons to explain this discrepancy.

While medications with other mechanisms of action (such as interleukin-6 inhibitors) are also used for the treatment of refractory JIA associated uveitis, the panel did not feel confident in extrapolating the findings from this review to non-TNF-α bDMARDs or tsDMARDs.

The panel was strongly of the view that the benefits of adalimumab treatment were easily balanced by the burden of an injectable immunosuppressant medication, but that the decision to use it would be influenced by individual circumstances, preferences and values, and that a continuous, open and informed shared decision-making process should underpin any such decision. The panel considered the significant cost of adalimumab but still favoured it as a cost effective option given the risk of permanent ocular damage and lack of more cost effective, evidence based alternative treatments. The panel highlighted the importance of equitable access to high quality care including such treatments.

Clinical Question/ PICO

Population: Children and young people with a diagnosis of juvenile idiopathic arthritis (JIA) as per the International League Against Rheumatism (ILAR) criteria or earlier equivalents who have JIA associated uveitis that is inadequately controlled by methotrexate

Intervention: Any biologic or targeted synthetic disease modifying anti-rheumatic drug

Comparator: Placebo

Outcome Timeframe	**Study results and measurements**	**Comparator** Placebo	**Intervention** b/tsDMARD	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Number with treatment response / success of uveitis 9 Critical	Relative risk 2.57 (CI 95% 1.39 — 4.74) Based on data from 133 patients in 3 studies. [1] (Randomized controlled) Follow up: 18 months.	**200** per 1000 Difference:	**514** per 1000 **314 more per 1000** (CI 95% 78 more — 748 more)	**Low** Due to serious indirectness and imprecision [2]	b/tsDMARDs may increase the likelihood of achieving treatment response.
Number with treatment failure / flare of uveitis 9 Critical	Relative risk 0.47 (CI 95% 0.28 — 0.77) Based on data from 102 patients in 2 studies. [3] (Randomized controlled) Follow up: 18 months.	**514** per 1000 Difference:	**242** per 1000 **272 fewer per 1000** (CI 95% 370 fewer — 118 fewer)	**Low** Due to serious indirectness and imprecision [4]	b/tsDMARDs may decrease the likelihood of a uveitis flare.
Number of affected eyes with AC cell count improvement	Relative risk 0.63 (CI 95% 0.12 — 3.24) Based on data from 31 patients in 1 studies. [5] (Randomized controlled) Follow up: 2 months.	**200** per 1000 Difference:	**126** per 1000 **74 fewer per 1000**	**Low** Due to serious indirectness, Due to serious imprecision [6]	b/tsDMARDs may have little or no effect on the number of eyes with improvement in AC cell count.

Outcome Timeframe	**Study results and measurements**	**Comparator** Placebo	**Intervention** b/tsDMARD	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
9 Critical			(CI 95% 176 fewer — 448 more)		
Number who reduced topical steroid treatment to 2 or less drops/ day 9 Critical	Relative risk 3.07 (CI 95% 1.05 — 8.96) Based on data from 63 patients in 1 studies. (Randomized controlled) Follow up: 18 months.	167 per 1000 Difference:	513 per 1000 **346 more per 1000** (CI 95% 8 more — 1,329 more)	**Low** Due to serious indirectness and imprecision [7]	b/tsDMARDs may increase the likelihood of weaning topical steroid drops to two or less per day.
Number of new structural ocular comorbidities 9 Critical	Relative risk 0.94 (CI 95% 0.06 — 13.68) Based on data from 31 patients in 1 studies. [8] (Randomized controlled) Follow up: 2 months.	67 per 1000 Difference:	63 per 1000 **4 fewer per 1000** (CI 95% 63 fewer — 850 more)	**Very low** Due to serious indirectness and imprecision. [9]	We are uncertain whether b/tsDMARDs use results in less people developing new structural ocular comorbidities.
Serious adverse events 9 Critical	Relative risk 1.55 (CI 95% 0.23 — 10.63) Based on data from 133 patients in 3 studies. [10] (Randomized controlled) Follow up: 18 months.	80 per 1000 Difference:	124 per 1000 **44 more per 1000** (CI 95% 62 fewer — 770 more)	**Low** Due to serious indirectness and imprecision [11]	b/tsDMARDs may have little or no effect on the number of serious adverse events.
Mean patient global assessment of disease activity	Based on data from 0 patients in 0 studies.		CI 95%		
Mean CHAQ	Based on data from 0 patients in 0 studies.		CI 95%		
Visual acuity (logMAR) 9 Critical	Measured by: Visual acuity Scale: -0.3 — 2 Lower better Based on data from: 63 patients in 1 studies. [12] (Randomized controlled) Follow up: 6 months.	0.07 logMAR (Mean) Difference:	0.02 logMAR (Mean) **MD 0.05 lower** (CI 95% 0.17 lower — 0.7 higher)	**Very low** Due to serious indirectness and imprecision. [13]	We are uncertain whether b/tsDMARDs use has an effect on visual acuity.

1. Primary study. **Baseline/comparator:** Control arm of reference used for intervention. **Supporting references:** [3], [2], [1],
2. **Inconsistency: no serious. Indirectness: serious.** DMARD use limited to etanercept (in 1 trial) and adalimumab (in 2 trials).. **Imprecision: serious.** Small event rate.. **Publication bias: no serious.**
3. Systematic review. **Baseline/comparator:** Control arm of reference used for intervention. **Supporting references:** [3], [2],

4. **Inconsistency: no serious. Indirectness: serious.** DMARD use limited to etanercept (in 1 trial) and adalimumab (in 2 trials).. **Imprecision: serious.** Small event rate.. **Publication bias: no serious.**
5. Systematic review. **Baseline/comparator:** Control arm of reference used for intervention. **Supporting references:** [3],
6. **Inconsistency: no serious. Indirectness: serious.** DMARD use limited to etanercept (in 1 trial) and adalimumab (in 2 trials).. **Imprecision: serious.** Small event rate.. **Publication bias: no serious.**
7. **Inconsistency: no serious. Indirectness: serious.** DMARD use limited to etanercept (in 1 trial) and adalimumab (in 2 trials). **Imprecision: serious.** Small event rate.. **Publication bias: no serious.**
8. Systematic review. **Baseline/comparator:** Control arm of reference used for intervention. **Supporting references:** [1],
9. **Inconsistency: no serious. Indirectness: serious.** DMARD use limited to etanercept (in 1 trial) and adalimumab (in 2 trials). Included participants with low disease activity. Short follow up time.. **Imprecision: serious.** Small event rate. Short follow up time.. **Publication bias: no serious.**
10. Systematic review. **Baseline/comparator:** Control arm of reference used for intervention. **Supporting references:** [3], [2], [1],
11. **Inconsistency: no serious. Indirectness: serious.** DMARD use limited to etanercept (in 1 trial) and adalimumab (in 2 trials)., Differences between the population of interest and those studied, The outcome time frame in studies were insufficient. **Imprecision: serious.** Small event rate.. **Publication bias: no serious.**
12. Systematic review. **Baseline/comparator:** Control arm of reference used for intervention. **Supporting references:** [2],
13. **Inconsistency: no serious. Indirectness: serious.** DMARD use limited to etanercept (in 1 trial) and adalimumab (in 2 trials). Included participants with low disease activity. Short follow up time., The outcome time frame in studies were insufficient. **Imprecision: serious.** Small event rate.. **Publication bias: no serious.**

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