

Biological disease-modifying antirheumatic drugs in juvenile idiopathic arthritis of polyarticular course, enthesitis-related arthritis, and psoriatic arthritis: a consensus statement

Assunta CH Ho *, SN Wong, Lettie CK Leung, Winnie KY Chan, Patrick CY Chong, Niko KC Tse, Roanna HM Yeung, SY Kong, KP Lee

ABSTRACT

Objectives: Juvenile idiopathic arthritis (JIA) is the most common type of inflammatory arthritis in children. Treatment options have been expanded since the introduction of biologics, which are highly effective. The existing local JIA treatment guideline was published more than a decade ago, when use of biologics was not as common. In this article, we review the latest evidence on using biologics in three JIA subtypes: JIA of polyarticular course (pcJIA), enthesitis-related arthritis (ERA), and psoriatic arthritis (PsA). Based on the latest information, an update on eligibility, response assessment, termination, and safety information for using biologics in these patients was performed.

Consensus process: The JIA Work Group, which consisted of nine paediatricians experienced in managing JIA, was convened in 2016. Publications before July 2017 were screened. Eligible articles were clinical trials, extension studies, systemic reviews, and recommendations from international societies and regulatory agencies about the use of biologics in pcJIA, ERA, and PsA. Evidence extraction, appraisal, and drafting of propositions were performed by two reviewers. Extracted evidence and drafted propositions were presented and discussed at the first two meetings. Overwhelming consensus was obtained at the final meeting in May 2018. Seven

practice consensus statements were formulated. Regular review should be performed to keep the practice evidence-based and up-to-date.

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Introduction

Biological disease-modifying antirheumatic drugs (DMARDs) were introduced for the treatment of juvenile idiopathic arthritis (JIA) in year 2000. They are highly effective, especially for patients who are refractory to conventional DMARDs (cDMARDs). The current treatment algorithm for JIA in Hong Kong was published more than a decade ago, when the use of biologics was not as common.¹ There has been a huge expansion in knowledge and approved medications since then. An update of practice based on the latest evidence is required, not only for specialists but also paediatricians and family physicians who may provide care to children with JIA.

The Hong Kong Society for Paediatric

Rheumatology commissioned the JIA Work Group in 2016 to review this topic. The work group consists of nine paediatricians experienced in managing JIA. Our aims were: (1) to review the latest evidence on biological DMARDs in polyarticular course JIA (pcJIA, ie, those having arthritis affecting ≥5 joints irrespective of subtype at onset), enthesitis-related arthritis (ERA), and psoriatic arthritis (PsA); and (2) to propose an updated practice consensus for using biologics in these patients.

Methods

Articles about the use of biologics in pcJIA, ERA, and PsA published in English before July 2017 were identified by searching MEDLINE and PubMed. The keywords used for searching included JIA,

pcJIA, ERA, PsA, eoJIA (extended oligoarticular arthritis), biologics, biological DMARDs, guidelines, recommendation, practice review, registries, adverse effects, malignancy, and infection. Publications considered relevant were clinical trials (randomised trials, reports on long-term extension phase of clinical trials), open-label studies, results from analysis of major registries, and recommendations from international regulatory organisations (United Kingdom: Clinical Commissioning Policy of National Health Service, National Institute for Health and Care Excellence; United States: American College of Rheumatology [ACR]; Australia: the Pharmaceutical Benefits Scheme, reimbursement programme for biologics use). Article screening, grading of the level of evidence, and propositions drafting were performed by two reviewers. The extracted evidence and draft propositions were presented to work group members at the first meeting held in July 2017. They were discussed and deliberated in a subsequent meeting held in March 2018. At the final meeting in May 2018, overwhelming consensus was reached on seven practice consensus statements.

Statement 1: Level of care

Care of children with JIA should preferably be shared jointly with paediatricians experienced in managing JIA.

With modern treatment strategies, a high level of disease control is possible. One study reported that more than 70% of patients (except rheumatoid factor positive polyarticular JIA) were able to reach a clinically inactive disease state within 2 years.² To achieve the best outcome, care plans and treatment targets should be carefully formulated together with patients and paediatricians experienced in managing JIA.

Statement 2: Therapeutic ladder

For pcJIA, ERA and PsA, patients with persistently active arthritis despite adequate use of one or more cDMARDs, or if patients are intolerant of them, treatment escalation to biological DMARDs should be considered.

Conventional DMARDs like methotrexate, leflunomide, and sulphasalazine are effective in treating pcJIA.³⁻⁶ The choice of cDMARDs usually depends on JIA subtype and patient tolerance. Nevertheless, some patients may not respond to or may be intolerant of cDMARDs. Switching to biologics should be considered in these cases.

Biological disease-modifying antirheumatic drugs: evidence of effectiveness

Anti-tumour necrosis factor inhibitors

Etanercept

Etanercept is a chimeric fusion protein that acts

有關生物製劑於多關節型的幼年突發性關節炎、附着點炎症相關關節炎及銀屑病關節炎的運用：共識聲明

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目的：幼年突發性關節炎(簡稱JIA)是最常見的兒童關節炎。隨着生物製劑的引入，現代的治療方案比過往更有效。本港上一份治療方案沿用至今已有十多年，那時生物製劑的使用並未普遍。本文探討生物製劑於三款關節炎的使用，包括多關節型的幼年突發性關節炎(polyarticular course JIA)、附着點炎症相關關節炎(enthesitis related arthritis, ERA)及銀屑病關節炎(psoriatic arthritis, PsA)。本文亦會根據最新的科研資料及參考國際權威機構的治療建議，提供最新的治療準則。

共識過程：九位富有治療關節炎經驗的兒科醫生於2016年組成工作小組。小組分析2017年7月前刊載的相關文獻、研究論文、薈萃分析、指南及共識聲明，並在會議前預備共識聲明草案。經過兩次會議及討論，小組最終確定七項共識聲明。此聲明須定期檢視最新證據以及更新。

as soluble TNF receptor. It is approved for use in cases of: (1) pcJIA in children aged ≥ 2 years (Food and Drug Administration [FDA] and European Medicines Agency [EMA]) and (2) ERA and PsA in children aged ≥ 12 years (EMA). The dose is 0.4 mg/kg (max 25 mg) twice weekly or 0.8 mg/kg (max 50 mg) once weekly subcutaneously.

Etanercept was the first anti-TNF inhibitor approved for pcJIA. Its efficacy was demonstrated by a randomised withdrawal trial⁷, in which 69 patients with pcJIA aged 4 to 17 years who were refractory to methotrexate were enrolled in the open-label lead-in phase. Fifty one (74%) patients achieved an ACR 30 response at week 12. They were then randomised to receive either etanercept or placebo for 16 weeks. Etanercept was more effective in preventing arthritis flares (28% vs 81%, $P=0.003$). The median time to flare was significantly shorter in the placebo group (28 days vs 116 days, $P<0.001$). Long-term data from the extension phase confirmed the persistence of efficacy.⁸

The use of etanercept in eoJIA, ERA, and PsA was studied by Horneff et al.⁹ In all, 127 patients (60 patients with eoJIA aged 2-17 years, 38 patients with ERA aged 12-17 years, 29 patients with PsA aged 12-17 years) were recruited in an open-label multicentre study. All had persistently active disease despite the use of nonsteroidal anti-inflammatory drugs (NSAIDs; for ERA) and DMARDs (for eoJIA, ERA, and PsA). At week 12, 88.6% (95% confidence interval [CI]=81.6%-93.6%) had attained ACR 30 response. The proportion of response was similar across all three subtypes.

The efficacy of etanercept in ERA was further evaluated. In a phase III double-blinded study, 41 patients aged 6 to 17 years with active disease despite taking at least one NSAID and one DMARD were recruited. They received open-label etanercept for 24 weeks. An ACR 30 response was achieved in 38 (93%). These patients were then randomised to receive etanercept or placebo in the subsequent 24-week withdrawal phase. The odds for having a flare was significantly higher in placebo group (odds ratio=6, 95% CI=1.1-37, $P=0.02$).¹⁰

The use of etanercept has now been extended to 2 years old.¹¹ The efficacy of administering at 0.8 mg/kg weekly has been shown to be comparable to twice weekly dosing.¹²

Etanercept can be used concomitantly with methotrexate or as monotherapy.¹³

Adalimumab

Adalimumab is a fully humanised monoclonal anti-TNF antibody. It is approved for use in cases of: (1) pcJIA in children aged ≥ 2 years (FDA and EMA) and (2) ERA in children aged ≥ 6 years (EMA). The dose is once every other week at 10 mg for 10 to <15 kg, 20 mg for 15 to <30 kg, and 40 mg for ≥ 30 kg.

Adalimumab was shown to be effective in treating pcJIA by Lovell et al.¹⁴ In total, 171 patients aged 4 to 17 years with active arthritis despite taking NSAIDs or methotrexate were enrolled in the 16-week open-label phase. In all, 94% of the adalimumab-methotrexate group and 74% of the adalimumab monotherapy group demonstrated an ACR 30 response. In the 32-week randomised withdrawal phase, the flare rate was significantly lower for those who remained on adalimumab. The results were more pronounced in patients receiving concomitant methotrexate (flare in placebo and methotrexate vs adalimumab and methotrexate: 65% vs 37%, $P=0.02$; flare in placebo vs adalimumab: 71% vs 43%, $P=0.03$). Efficacy was maintained in the long-term extension phase.

Burgos-Vargas et al¹⁵ studied the effectiveness of adalimumab in 46 patients with ERA. These patients, aged 6 to 17 years, had active arthritis and enthesitis. They were randomised to receive either adalimumab or placebo. At week 12, the adalimumab group had a significantly greater percentage decrease in the number of active joints (-62.2% vs -11.6%, $P=0.039$).

The safety and effectiveness of adalimumab in children aged 2 to 4 years weighing <15 kg were also demonstrated.¹⁶

Adalimumab can be used together with methotrexate or as monotherapy.

T cell co-stimulation inhibitor

Abatacept

Abatacept is a co-stimulation modulator that binds

to the cluster of differentiation (CD) 80 or CD 86 ligands of the antigen-presenting cell and interferes with its interactions with T cells. Abatacept is indicated for pcJIA in children aged ≥ 6 years who are unresponsive to cDMARDs and at least one anti-TNF (EMA, FDA). The dose is 10 mg/kg (max 1g) infusion on day 1, 15, 29, and then every 28 days.

The efficacy of abatacept in pcJIA was assessed in a randomised withdrawal trial by Ruperto et al.¹⁷ The enrolled patients were aged 6 to 17 years with active disease despite DMARDs including anti-TNF inhibitors. Systemic JIA patients without systemic manifestations were also eligible. Patients with ERA or PsA were not included. Among the 190 recruited patients, 27% had previously been exposed to anti-TNF therapy. At the end of the 4-month open-label phase, 123 (65%) demonstrated an ACR 30 response. After one patient left the study, the remaining 122 patients were randomised to receive abatacept (60 patients) or placebo (62 patients) for 6 months. The flare rate of the abatacept group was significantly lower than that of the placebo group (20% vs 53%, $P=0.0003$). The hazard ratio for having a flare in the abatacept group was 0.31 (95% CI=0.16-0.95). The median time to flare was 6 months for placebo and not assessable for abatacept because of an inadequate number of events ($P=0.0002$). Among patients who did not achieve ACR 30 at the end of the 4-month open-label phase, half achieved ACR 30 after longer exposure. By day 589 of the long-term extension phase, the proportions of patients achieving ACR 30, 50, 70, 90, and 100 were 90%, 88%, 75%, 57%, and 39%, respectively.¹⁸

Abatacept can be used concomitantly with methotrexate or as monotherapy.

Anti-interleukin 6 inhibitor

Tocilizumab

Tocilizumab is a humanised anti-interleukin 6 monoclonal antibody. It is indicated for pcJIA in child aged ≥ 2 years (FDA, EMA). The dose is once every 4 weeks intravenous infusion, 10 mg/kg for <30 kg, 8 mg/kg for ≥ 30 kg.

Tocilizumab is another non-anti-TNF option for pcJIA. In a phase 3, three-part randomised controlled study (CHERISH), 188 patients aged 2 to 17 years with active disease received open-label tocilizumab for 16 weeks. In all, 166 (88%) achieved an ACR 30 response. A total of 163 were then randomised to receive tocilizumab ($n=82$) or placebo ($n=81$) for 24 weeks. Flares of JIA occurred significantly less often in the tocilizumab group (25.6% vs 48.1%, difference in means adjusted for stratification -0.21; 95% CI= -0.35 to -0.08; $P=0.0024$). Numerically more patients on concurrent methotrexate achieved ACR 70 and 90 responses.¹⁹

Tocilizumab can be used concomitantly with methotrexate or as monotherapy.

TABLE I. Summary of trials on individual biologics for pcJIA, ERA, and PsA

Author, year	Study design, sample size, duration	Drugs, comparator	Population	Concomitant MTx	Primary outcome	Results	Level of evidence*
Lovell, 2000 ⁷	12-week open-label lead-in phase, n=69 16-week randomised withdrawal trial for those who achieved ACR 30, n=51	Etanercept sc 0.4 mg/kg/dose 2x/week Max 25 mg vs placebo	pcJIA (eoJIA, PJIA, SJIA) Aged 4-17 years Active polyarthritis despite MTx ≥ 10 mg/m ² /week (active arthritis: ≥ 5 swollen and ≥ 3 LOM)	No	No. of patients with disease flare during randomised withdrawal phase	Placebo 81% (21 of 26) vs etanercept 28% (7 of 25), P=0.003	2
Horneff, 2014 ⁹	12-week open-label study, n=127 (60 eoJIA, 38 ERA, 29 PsA)	Etanercept sc 0.8 mg/kg/week, max 50 mg	eoJIA: aged 2-17 years ERA and PsA: aged 12-17 years Active disease: ≥ 2 active joints, history of intolerance or unsatisfactory response to at least 3 months of ≥ 1 DMARD or, only for ERA, at least 1 month of ≥ 1 NSAID	Allowed (one of the following allowed: MTx, SSZ, HCQ, chloroquine)	Percentage of patients achieving JIA ACR 30 at week 12	Overall: 88.6% (95% CI=81.6%-93.6%) eoJIA: 89.7% (95% CI=78.8%-96.1%) ERA: 83.3% (95% CI=67.2%-93.6%) PsA: 93.1% (95% CI=77.2%-99.2%)	3
Horneff, 2015 ¹⁰	24-week open-label lead-in phase, n=41 24-week randomised withdrawal trial for those who achieved ACR Pedi 30, n=38	Etanercept sc 0.8 mg/kg/week Max 50 mg vs placebo	ERA, aged 6-17 years Active disease: ≥ 3 active joints (swollen or LOM), NRS ≥ 3 for physician global disease activity and parents' overall well-being, intolerant of or failed ≥ 1 of DMARD and NSAID	No (SSZ allowed)	Disease flare during randomised withdrawal phase	Placebo: 9 of 18 vs etanercept: 3 of 20 OR=6, P=0.02 (95% CI=1.1-37)	2
Lovell, 2008 ¹⁴	16-week open-label lead-in phase, n=171 32-week randomised withdrawal phase for those who achieved ACR Pedi 30, n=144 Open-label extension phase	Adalimumab sc 24 mg/m ² every other week, max 40 mg vs placebo During open-label extension: 20 mg for BW <30 kg; 40 mg for BW ≥ 30 kg	pcJIA (any type of onset) Aged 4-17 years Active disease: ≥ 5 swollen and 3 LOM, inadequate response to or intolerant of NSAIDs with or without \pm MTx	Allowed	Disease flare in those not receiving MTx during randomised withdrawal phase	Those not on MTx: adalimumab 13/30 (43%) vs placebo 20/28 (71%), P=0.03 Those on MTx: adalimumab + MTx 14/38 (37%) vs placebo + MTx 24/37 (65%), P=0.02	2
Burgos-Vargas, 2015 ¹⁵	12-week randomised trial, n=46 192-week open-label extension	Adalimumab sc 24 mg/m ² every other week Max 40 mg vs placebo	ERA, aged 6-17 years Active disease: ≥ 3 active joints and ≥ 1 enthesitis, inadequate response to or intolerant of ≥ 1 NSAID and ≥ 1 DMARD (SSZ/MTx) (Active joint: swelling or LOM)	Allowed (SSZ also allowed)	Mean percentage change in active joint count from baseline to week 12	Adalimumab: -62.2% vs placebo: -11.6%, P=0.039	2

Abbreviations: 95% CI=95% confidence interval; ACR = American College of Rheumatology; BW = body weight ; DMARDs = disease-modifying antirheumatic drugs; eoJIA = extended oligoarticular JIA; ERA = enthesitis-related arthritis; HCQ = hydroxychloroquine; iv = intravenous; JIA = juvenile idiopathic arthritis; LOM = limitation in range of movement; MTx = methotrexate; NRS = numeric rating scale score; NSAIDs = nonsteroidal anti-inflammatory drugs; OR = odds ratio; pcJIA = polyarticular course JIA; PJIA = polyarticular JIA; PsA = psoriatic arthritis; sc = subcutaneous; SJIA = systemic JIA; SSZ = sulphasalazine

* OCEBM Level of Evidence Working Group. "The Oxford 2011 Levels of Evidence". Oxford Centre for Evidence-based Medicine. (<http://www.cebm.net/index.aspx?o=5653>)

TABLE 1. (cont'd)

Author, year	Study design, sample size, duration	Drugs, comparator	Population	Concomitant MTx	Primary outcome	Results	Level of evidence*
Ruperto, 2008 ¹⁷	16-week open-label lead-in phase, n=190 24-week randomised withdrawal phase for those who achieved ACR 30, n=122 5-year open-label extension	Abatacept 10 mg/kg iv in over 30 mins Max 1 g, on days 1, 15, and 29, then every 28 days vs placebo	pcJIA (eoJIA, PJIA, SJIA without systemic features) Aged 6-17 years At least 5 active joints and active disease (2 active and 2 LOM), inadequate response or intolerant of DMARDs including anti-TNF	Allowed	Time to flare during randomised withdrawal phase	Significantly shorter time to flare for placebo Placebo group: median time 6 months vs insufficient event for abatacept, P=0.0002 Risk of flare, hazard ratio=0.31; 95% CI=0.16-0.95	2
Brunner, 2015 ¹⁹	16-week open-label lead-in phase, n=188 24-week randomised withdrawal phase for those who achieved ACR 30, n=163 64-week open-label extension phase	Tocilizumab iv BW <30 kg: randomised to either 8 mg/kg or 10 mg/kg, every 4 weeks BW ≥30 kg: 8 mg/kg, every 4 weeks vs placebo	pcJIA (PJIA, eoJIA) Aged 2-17 years At least 5 active joints (swelling or LOM) and LOM in ≥3 active joints Inadequate response to or intolerant of MTx Previous use of biologics was allowed	Allowed	Disease flare during randomised withdrawal phase	Placebo: 39/81 (48.1%) vs tocilizumab: 21/82 (25.6%) Adjusted difference in flare rate: -0.21; 95% CI= -0.35 to -0.08 P=0.0024	2

Systemic reviews of biologics

The short-term efficacies of biologics have been confirmed by systemic reviews.²⁰⁻²² While there have been no head-to-head trials between individual biologics, analysis with indirect comparisons has not shown obvious differences in efficacy. Longer-term data (mainly for etanercept) and reports from major registries also confirm biologics' effectiveness and safety.²³ The results of clinical trials are summarised in Table 1.

Statement 3: Eligibility criteria for using biological disease-modifying antirheumatic drugs

The work group achieved overwhelming consensus on the following eligibility criteria.

Eligible conditions, age, and biologics

Table 2 lists the JIA subtypes and the corresponding biological DMARDs indicated. Anti-TNF inhibitors are usually the first biologics to commence, except in systemic JIA. The decision of which biologic to start also depends on JIA subtype, the presence of extra-articular manifestations (eg, uveitis, inflammatory bowel disease), patient preferences, etc.^{24,25}

Definition of adequate use of conventional disease-modifying antirheumatic drugs

- Patients should have been treated with at least

one cDMARD at adequate dose for at least 3 months unless toxicities are present.

- Use of intra-articular steroid injections or a short course of bridging systemic corticosteroids are acceptable during trial use of cDMARDs.
- In addition to cDMARDs, at least one anti-TNF inhibitor should have been tried before starting abatacept.

It usually takes 6 to 8 weeks before the effects of cDMARDs can be seen. "Adequate cDMARDs exposure" is often defined as at least 3 months. However, if one develops significant intolerance or toxicities during trial of cDMARDs, use of biologics should be considered earlier.

Definition of persistently active disease

- pcJIA: Five or more joints with active arthritis
- ERA and PsA: three or more joints with active arthritis

"Active arthritis" is defined as swelling, with or without limitation in movement. Joints with limitation in movement due to pain or tenderness are also considered as "active", especially those in which swelling is difficult to assess.

When deciding the number of joints required to define active disease, the work group adopted the commonly used inclusion criteria of the clinical trials. In view of the fact that the disease characteristics (eg, number of joints involved, clinical course, medication indicated) are somewhat different for

ERA and PsA, the work group considered it more appropriate to have separate definitions for ERA and PsA.

Statement 4: Assessment of response

- Assessment of response to biological DMARDs should be performed after adequate exposure. For etanercept, adalimumab and tocilizumab, assessment should take place at 16 weeks. For abatacept, assessment at 24 weeks is acceptable if the expected response is not reached by 16 weeks.
- A 50% reduction of the initial active joint count (≥ 2 joints) is considered as a positive response.

Patients usually experience improvement within or around 3 months after commencement. The exception is abatacept, which may take a bit longer to achieve the desired therapeutic effect.²⁰

The definition of positive response is extrapolated from Pharmaceutical Benefits Scheme. It is easy to apply and does not require inflammatory markers like erythrocyte sedimentation rate and C-reactive protein, as they are not always elevated.

Statement 5: Termination of treatment

Termination of treatment should be considered in the following situations:

- Toxicities or medical conditions that contra-indicate further use of biologics, including but not limited to severe injection reaction, severe infection, malignancy, demyelination, heart failure, etc
- Pregnancy (temporary withdrawal may be appropriate for anti-TNF inhibitors)
- Lack of 50% reduction in the number of joints with active arthritis after the 16th week (or 6th month for abatacept)
- Persistent inactive disease state, defined as Clinical Juvenile Arthritis Disease Activity Score ≤ 1 , for at least 1 year

The above termination criteria represent the common “end points” for stopping biologics, ie, the development of side-effects, conditions contra-indicated for use of biologics, or continuous remission of the index disease.

Pregnancy is no longer an absolute contra-indication in adult patients with rheumatoid arthritis or ankylosing spondylitis who are receiving anti-TNF inhibitors. Temporary withdrawal, however, is necessary for some agents. There have been no recent updates from international organisations on the use of biologics in pregnant patients with JIA. This issue should be revisited during the next update.

Several definitions are used to describe treatment response and disease remission in JIA.²⁶

TABLE 2. Eligibility: age, subtype, and biologics

JIA subtype	Biologics
pcJIA ≥ 2 years	Etanercept Adalimumab Tocilizumab (eoJIA, PJIA)
pcJIA who fail to response to ≥ 1 cDMARD and ≥ 1 anti-TNF inhibitor, aged ≥ 6 years (including eoJIA, PJIA, SJIA without active systemic features)	Abatacept
ERA ≥ 12 years	Etanercept, adalimumab
ERA ≥ 6 years	Adalimumab
PsA ≥ 12 years	Etanercept

Abbreviations: cDMARDs = conventional disease-modifying antirheumatic drugs; eoJIA = extended oligoarticular JIA; ERA = enthesitis-related arthritis; JIA = juvenile idiopathic arthritis; pcJIA = polyarticular course JIA; PJIA = polyarticular JIA; PsA = psoriatic arthritis; SJIA = systemic JIA; TNF = tumour necrosis factor

The Clinical Juvenile Arthritis Disease Activity Score is a composite measurement that evaluates three variables: active joint count, patient’s/parents’ global well-being score, and physician’s global disease activity score (both on visual analogue scales). It has been shown to outperform other activity measurements in predicting the need of escalation to anti-TNF inhibitors.²⁷ For both oligoarticular arthritis and pcJIA, a score of ≤ 1 signifies inactive disease.

Statement 6: Malignancy and infection

- The risk of developing new-onset malignancy due to exposure to biological DMARDs is low. Careful screening and close monitoring are recommended.
- Patients on biological DMARDs should follow vaccination schedules according to local recommendations except for live attenuated vaccines. Infection screening should be performed prior to commencement. Screening should include (but not be limited to) tuberculosis, hepatitis B and C. Individual risk profiles should also be taken into consideration.

In 2008, the FDA issued a black box warning about the development of malignancy, particularly lymphoproliferative types, in 48 children after commencement of anti-TNF inhibitors between 2001 and 2008.²⁸ In recent years, researchers investigated the risk of malignancy by analysing data generated from major registries and medical reimbursement databases. These data suggested that TNF inhibition alone is probably not causing the apparent increase in incident malignancy. Instead, those children’s background risk might have already been elevated compared with that of the general population. Nevertheless, much longer-term data on larger patient samples are needed, as both cancer and JIA are rare in children.²⁹⁻³¹

Data on the associations between malignancy and other non-anti-TNF biologics are still lacking. Careful screening prior to commencement and ongoing surveillance are necessary.

As for infection, biological DMARDs are generally safe. Most infections associated with the use of biologics are mild. Nevertheless, data from registries and medical insurance databases did show an increase in bacterial or serious infections associated with TNF inhibition.³²⁻³⁴ Tuberculosis is a genuine concern in our locality.^{35,36} Careful screening and follow-up according to individual risk profiles is strongly encouraged. The baseline infection screening should include, but not be limited to, the following:

- Tuberculosis: Mantoux test, chest X-ray, interferon-gamma release assay
- Hepatitis screening: hepatitis B surface antigen, antibody to hepatitis B core antigen, antibody to

hepatitis C antigen

While live attenuated vaccines should be avoided during use of biologics, patients should follow local guidelines for non-live vaccines.

Statement 7: Special consideration

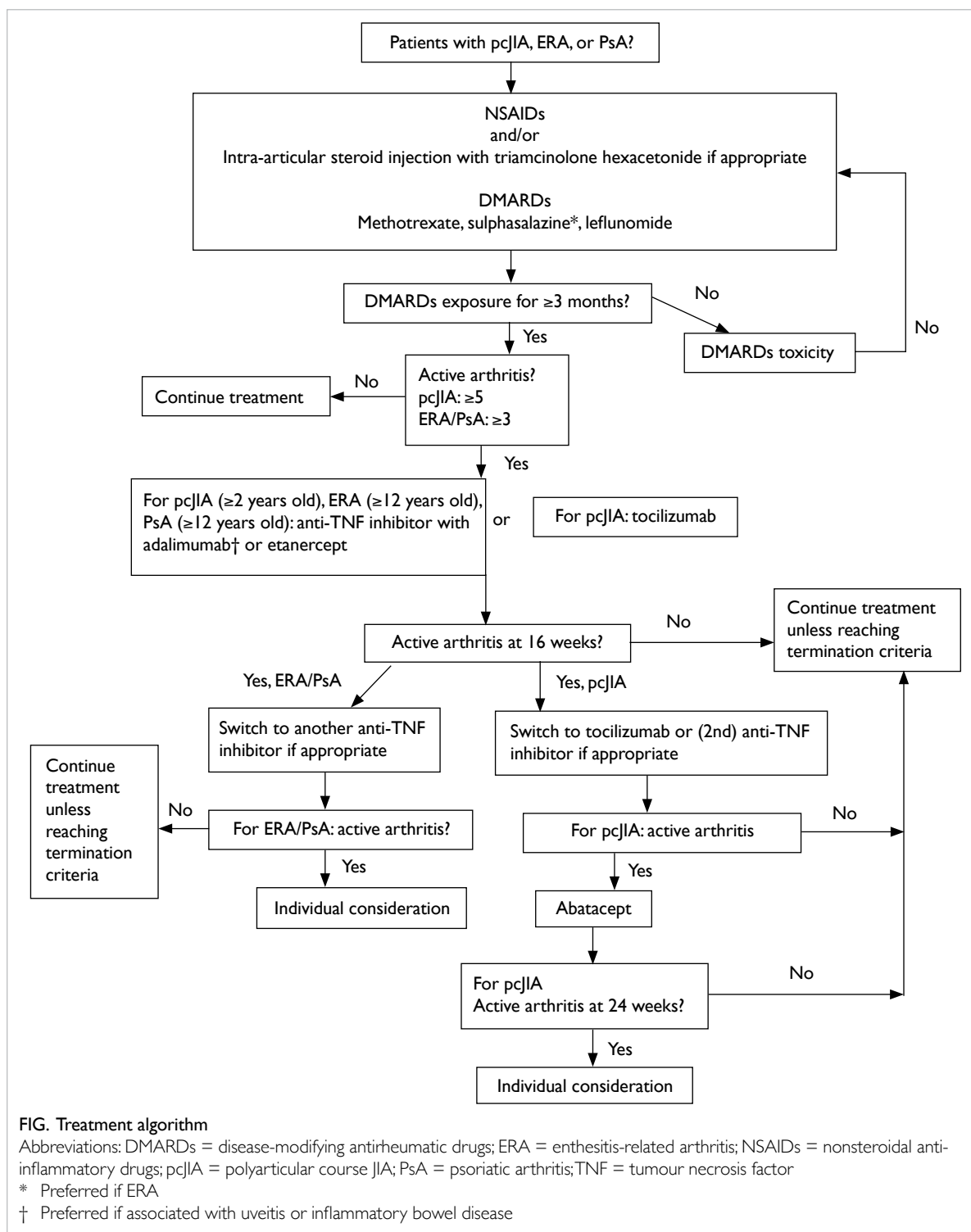
- **For patients with refractory disease but who do not fulfil the above criteria, biologics can be considered on a case-by-case basis.**

The work group is aware that some patients who do not fulfil the above criteria might still benefit from biologics. These patients include those with persistently active and disabling multiple enthesitis or sacroiliitis despite NSAIDs and DMARDs or oligoarticular JIA with severely active arthritis and has exhausted treatment modalities including intra-articular steroid injections and multiple cDMARDs, etc. The use of biologics can be

TABLE 3. Summary of key consensus

Consensus statements
<p>Statement 1: Level of care Care of children with JIA should preferably be shared jointly with paediatricians experienced in managing JIA.</p>
<p>Statement 2: Therapeutic ladder For pcJIA, ERA and PsA, patients with persistently active arthritis despite adequate use of ≥ 1 cDMARD, or if patients are intolerant of them, treatment escalation to biological DMARDs should be considered.</p>
<p>Statement 3: Eligibility criteria for using biological DMARDs</p> <p>(a) Eligible conditions, age, and biologics</p> <ul style="list-style-type: none"> • pcJIA aged ≥ 2 years: etanercept, adalimumab, tocilizumab (eoJIA, PJIA) • pcJIA (including eoJIA, PJIA, SJIA without active systemic features) who fail to response to ≥ 1 DMARD and ≥ 1 anti-TNF inhibitor, aged ≥ 6 years: abatacept • ERA: adalimumab (aged ≥ 6 years), etanercept (aged ≥ 12 years) • PsA: etanercept (aged ≥ 12 years) <p>(b) Definition of adequate cDMARD use</p> <ul style="list-style-type: none"> • Patient should have been treated with ≥ 1 cDMARD at adequate dose for ≥ 3 months unless toxicities are present. • Use of intra-articular steroid injections or a short course of bridging systemic corticosteroids are acceptable during trial use of cDMARDs. • In addition to cDMARDs, ≥ 1 anti-TNF inhibitor should have been tried before starting abatacept. <p>(c) Definition of persistently active disease</p> <ul style="list-style-type: none"> • pcJIA: ≥ 5 joints with active arthritis • ERA and PsA: ≥ 3 joints with active arthritis
<p>Statement 4: Assessment of response</p> <ul style="list-style-type: none"> • Assessment of response to biological DMARDs should be performed after adequate exposure. For etanercept, adalimumab and tocilizumab, assessment should take place at 16 weeks. For abatacept, assessment at 24 weeks is acceptable if the expected response is not reached by 16 weeks. • A 50% reduction in the initial active joint count (≥ 2 joints) is considered as a positive response.
<p>Statement 5: Termination of treatment Termination of treatment should be considered in the following situations:</p> <ul style="list-style-type: none"> • Toxicities or medical conditions that contra-indicate further use of biologics (including but not limited to severe injection reaction, severe infection, malignancy, demyelination, heart failure, etc) • Pregnancy (temporary withdrawal may be appropriate for anti-TNF inhibitors) • Lack of 50% reduction in the number of joints with active arthritis after the 16th week (or 6th month for abatacept) • Persistent inactive disease state, defined as cJADAS ≤ 1, for ≥ 1 year
<p>Statement 6: Malignancy and infection</p> <ul style="list-style-type: none"> • The risk of developing new-onset malignancy due to exposure to biological DMARDs is low. Careful screening and close monitoring are recommended. • Patients on biological DMARDs should follow local recommendations for vaccination practices except for live attenuated vaccines. Infection screening should be performed prior to commencement. Screening should include (but not be limited to) tuberculosis and hepatitis B and C. Individual risk profiles should be taken into consideration.
<p>Statement 7: Special consideration For patients with refractory disease but who do not fulfil the above criteria, biologics can be considered on a case-by-case basis.</p>

Abbreviations: cDMARDs = conventional DMARDs; cJADAS = Clinical Juvenile Arthritis Disease Activity Score; DMARDs = disease-modifying antirheumatic drugs; eoJIA = extended oligoarticular JIA; ERA = enthesitis-related arthritis; JIA = juvenile idiopathic arthritis; pcJIA = polyarticular course JIA; PJIA = polyarticular JIA; PsA = psoriatic arthritis; SJIA = systemic JIA



considered after careful assessment on a case-by-case basis.

The key recommendations and treatment algorithm are summarised in Table 3 and the Figure.

Looking ahead: new indications after the review period

The indications for use of biological DMARDs have been expanding. For example, subcutaneous

abatacept and tocilizumab are approved for pcJIA in patients aged ≥ 2 years in the United States.³⁷⁻³⁹ The ACR is also preparing a new update of the 2011 and 2013 guidelines. A review of the practice should be performed regularly.

Conclusion

The use of biological DMARDs has greatly improved the management of patients with JIA. Both patients

and physicians could benefit from incorporating the latest and best available evidence into disease management. Periodic review should be performed to keep clinical practice evidence-based and up-to-date.

Author contributions

All the authors contributed substantially to conception and design, acquisition and analysis of data, drafting and revising the article, and approval of the version to be published.

Conflicts of interest

All authors have no competing interest in the products mentioned in this paper.

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