**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.

**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,
biologics should be considered in these cases. or may be intolerant of cDMARDs. Switching to nevertheless, some patients may not respond to depends on JIA subtype and patient tolerance. treating pcJIA.3-6 The choice of cDMARDs usually leflunomide, and sulphasalazine are effective in a clinically inactive disease state within 2 years.2 To that more than 70% of patients (except rheumatoid factor positive polyarticular JIA) were able to reach of disease control is possible. One study reported that more than 70% of patients (except rheumatoid arthritis (RA)) were able to reach an ACR 50 response. The proportion of response was similar across all three subtypes.

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.3-5 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 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.

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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).

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

Etanercept can be used concomitantly with methotrexate or as monotherapy.

**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. 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 vs 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 al 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.

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. 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.

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.
<table>
<thead>
<tr>
<th>Author, year</th>
<th>Study design, sample size, duration</th>
<th>Drugs, comparator</th>
<th>Population</th>
<th>Concomitant MTx</th>
<th>Primary outcome</th>
<th>Results</th>
<th>Level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lovell, 2000</td>
<td>12-week open-label lead-in phase, n=69</td>
<td>Etanercept sc 0.4 mg/kg/dose 2×/week</td>
<td>pcJIA (eoJIA, PJIA, SJIA)</td>
<td>No</td>
<td>No of patients with disease flare during randomised withdrawal phase</td>
<td>Placebo 81% (21 of 26) vs etanercept 28% (7 of 25), P=0.003</td>
<td>2</td>
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<tr>
<td></td>
<td>16-week randomised withdrawal trial for those who achieved ACR 30, n=51</td>
<td>Max 25 mg vs placebo</td>
<td>Aged 4-17 years</td>
<td>Active polyarthritis despite MTx ≥10 mg/m²/week (active arthritis: ≥5 swollen and ≥3 LOM)</td>
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<tr>
<td>Horneff, 2014</td>
<td>12-week open-label study, n=127 (60 eoJIA, 38 ERA, 29 PsA)</td>
<td>Etanercept sc 0.8 mg/kg/week, max 50 mg</td>
<td>eoJIA: aged 2-17 years</td>
<td>Allowed (one of the following allowed: MTx, SSZ, HCQ, chloroquine)</td>
<td>Percentage of patients achieving JIA ACR 30 at week 12</td>
<td>Overall: 88.6% (95% CI=81.6%-93.6%)</td>
<td>3</td>
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<tr>
<td></td>
<td></td>
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<td>ERA and PsA: aged 12-17 years</td>
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<td></td>
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<td></td>
<td>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</td>
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<tr>
<td>Horneff, 2015</td>
<td>24-week open-label lead-in phase, n=41</td>
<td>Etanercept sc 0.8 mg/kg/week</td>
<td>ERA, aged 6-17 years</td>
<td>No (SSZ allowed)</td>
<td>Disease flare during randomised withdrawal phase</td>
<td>Placebo: 9 of 18 vs etanercept: 3 of 20 OR=6, P=0.02 (95% CI=1.1-37)</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>16-week randomised withdrawal trial for those who achieved ACR Pedi 30, n=38</td>
<td>Max 50 mg vs placebo</td>
<td>Active disease: ≥3 active joints (swollen or LOM), NRS ≥3 for physician global arthritis activity and parents' overall well-being, intolerant of or failed ≥1 of DMARD and NSAID</td>
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<tr>
<td>Lovell, 2008</td>
<td>16-week open-label lead-in phase, n=171</td>
<td>Adalimumab sc 24 mg/m² every other week, max 40 mg vs placebo</td>
<td>pcJIA (any type of onset)</td>
<td>Allowed</td>
<td>Disease flare in those not receiving MTx during randomised withdrawal phase</td>
<td>Those not on MTx: adalimumab 13/30 (43%) vs placebo 20/28 (71%), P=0.03</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>32-week randomised withdrawal phase for those who achieved ACR Pedi 30, n=144</td>
<td>During open-label extension: 20 mg for BW &lt;30 kg; 40 mg for BW ≥30 kg</td>
<td>Aged 4-17 years</td>
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<tr>
<td></td>
<td>Open-label extension phase</td>
<td></td>
<td>Active disease: ≥5 swollen and 3 LOM, inadequate response to or intolerant of ≥1 NSAIDs with or without ≥1 MTx</td>
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<tr>
<td>Burgos-Vargas, 2015</td>
<td>12-week randomised trial, n=46</td>
<td>Adalimumab sc 24 mg/m² every other week</td>
<td>ERA, aged 6-17 years</td>
<td>Allowed (SSZ also allowed)</td>
<td>Mean percentage change in active joint count from baseline to week 12</td>
<td>Adalimumab: -62.2% vs placebo: -11.6%, P=0.039</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>192-week open-label extension</td>
<td>Max 40 mg vs placebo</td>
<td>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)</td>
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</table>

Abbreviations: 95% CI=95% confidence interval; ACR = American College of Rheumatology; BW = body weight; DMARDs = disease-modifying antirheumatic drugs; eoJIA = extended oligoarticular JIA; ERA = enthesis-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

TABLE 1. (cont’d)

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Study design, sample size, duration</th>
<th>Drugs, comparator</th>
<th>Population</th>
<th>Concomitant MTx</th>
<th>Primary outcome</th>
<th>Results</th>
<th>Level of evidence*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ruperto, 20087</td>
<td>16-week open-label lead-in phase, n=190</td>
<td>Abatacept 10 mg/kg iv in over 30 mins</td>
<td>pcJIA (eoJIA, PJIA, SJIA without systemic features)</td>
<td>Allowed</td>
<td>Time to flare during randomised withdrawal phase</td>
<td>Significantly shorter time to flare for placebo</td>
<td>2</td>
</tr>
<tr>
<td>Brunner, 201519</td>
<td>16-week open-label lead-in phase, n=188</td>
<td>Tocilizumab iv BW &lt;30 kg: randomised to either 8 mg/kg or 10 mg/kg, every 4 weeks</td>
<td>pcJIA (PJIA, eoJIA)</td>
<td>Allowed</td>
<td>Disease flare during randomised withdrawal phase</td>
<td>Placebo vs tocilizumab: 21/82 (25.6%)</td>
<td>2</td>
</tr>
</tbody>
</table>

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...
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ER A 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.

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 contraindicate 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 contraindicated for use of biologics, or continuous remission of the index disease.

Pregnancy is no longer an absolute contraindication 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.

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. 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.

<table>
<thead>
<tr>
<th>JIA subtype</th>
<th>Biologics</th>
</tr>
</thead>
<tbody>
<tr>
<td>pcJIA ≥2 years</td>
<td>Etanercept, adalimumab</td>
</tr>
<tr>
<td>pcJIA who fail to response to ≥1 cDMARD and ≥1 anti-TNF inhibitor, aged ≥6 years (including eoJIA, PJIA, SJIA without active systemic features)</td>
<td>Abatacept</td>
</tr>
<tr>
<td>ERA ≥12 years</td>
<td>Etanercept, adalimumab</td>
</tr>
<tr>
<td>ERA ≥6 years</td>
<td>Adalimumab</td>
</tr>
<tr>
<td>PsA ≥12 years</td>
<td>Etanercept</td>
</tr>
</tbody>
</table>

Abbreviations: cDMARDs = conventional disease-modifying antirheumatic drugs; eoJIA = extended oligoarticular JIA; ERA = enthesitis-related arthritis; JIA = juvenile idiopathic arthritis; pcJIA = polyarticular course JIA; PIJA = 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. For both oligoarticular arthritis and pcJIA, a score of ≤1 signifies inactive disease.
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.31,34 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

<table>
<thead>
<tr>
<th>Consensus statements</th>
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<tbody>
<tr>
<td><strong>Statement 1: Level of care</strong></td>
</tr>
<tr>
<td>Care of children with JIA should preferably be shared jointly with paediatricians experienced in managing JIA.</td>
</tr>
<tr>
<td><strong>Statement 2: Therapeutic ladder</strong></td>
</tr>
<tr>
<td>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.</td>
</tr>
<tr>
<td><strong>Statement 3: Eligibility criteria for using biological DMARDs</strong></td>
</tr>
<tr>
<td>(a) Eligible conditions, age, and biologics</td>
</tr>
<tr>
<td>- pcJIA aged ≥2 years: etanercept, adalimumab, tocilizumab (eoJIA, PJJIA)</td>
</tr>
<tr>
<td>- pcJIA (including eoJIA, PJJIA, SJIA without active systemic features) who fail to response to ≥1 DMARD and ≥1 anti-TNF inhibitor, aged ≥6 years: abatacept</td>
</tr>
<tr>
<td>- ERA: adalimumab (aged ≥6 years), etanercept (aged ≥12 years)</td>
</tr>
<tr>
<td>- PsA: etanercept (aged ≥12 years)</td>
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<tr>
<td>(b) Definition of adequate cDMARD use</td>
</tr>
<tr>
<td>- Patient should have been treated with ≥1 cDMARD at adequate dose for ≥3 months unless toxicities are present.</td>
</tr>
<tr>
<td>- Use of intra-articular steroid injections or a short course of bridging systemic corticosteroids are acceptable during trial use of cDMARDs.</td>
</tr>
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<td>- In addition to cDMARDs, ≥1 anti-TNF inhibitor should have been tried before starting abatacept.</td>
</tr>
<tr>
<td>(c) Definition of persistently active disease</td>
</tr>
<tr>
<td>- pcJIA: ≥5 joints with active arthritis</td>
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<td>- ERA and PsA: ≥3 joints with active arthritis</td>
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<td>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.</td>
</tr>
<tr>
<td>A ≥50% reduction in the initial active joint count (≥2 joints) is considered as a positive response.</td>
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<tr>
<td><strong>Statement 5: Termination of treatment</strong></td>
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<tr>
<td>Termination of treatment should be considered in the following situations:</td>
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<tr>
<td>- 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)</td>
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<td>- Pregnancy (temporary withdrawal may be appropriate for anti-TNF inhibitors)</td>
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<tr>
<td>- Lack of ≥50% reduction in the number of joints with active arthritis after the 16th week (or 6th month for abatacept)</td>
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<td>- Persistent inactive disease state, defined as cJADAS ≤1, for ≥1 year</td>
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<tr>
<td><strong>Statement 6: Malignancy and infection</strong></td>
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<tr>
<td>- The risk of developing new-onset malignancy due to exposure to biological DMARDs is low. Careful screening and close monitoring are recommended.</td>
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<tr>
<td>- 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.</td>
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<tr>
<td>Individual risk profiles should be taken into consideration.</td>
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<tr>
<td><strong>Statement 7: Special consideration</strong></td>
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<tr>
<td>For patients with refractory disease but who do not fulfil the above criteria, biologics can be considered on a case-by-case basis.</td>
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</tbody>
</table>

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; PJJIA = polyarticular JIA; PsA = psoriatic arthritis; SJIA = systemic JIA
Biologics in juvenile idiopathic arthritis

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. The ACR is also preparing a new update of the 2011 and 2013 guidelines. A review of the practice should be performed regularly.

Looking ahead: new indications after the review period

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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**References**

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