NHS England Evidence Review:

Canakinumab for patients with systemic-onset juvenile idiopathic arthritis (SJIA) refractory to anakinra and tocilizumab (adults and children 2 years and over)

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Canakinumab for patients with systemic-onset juvenile idiopathic arthritis (SJIA) refractory to anakinra and tocilizumab

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1. Introduction

This evidence review examines the clinical effectiveness, safety and cost effectiveness of canakinumab compared to current standard treatment in patients with systemic-onset juvenile idiopathic arthritis (SJIA) refractory to or intolerant of tocilizumab[1].

Canakinumab is a recombinant human monoclonal antibody that selectively inhibits the binding of interleukin-1 (IL-1) beta to its receptor. Canakinumab is given as a subcutaneous injection every 4 weeks. If patients do not respond to 1st, 2nd or 3rd line therapy, canakinumab is being proposed as a 4th line option.

First line treatment for SJIA consists of corticosteroids. Once the diagnosis is confirmed, a disease-modifying antirheumatic drug (DMARD), such as methotrexate, can be added for patients who fail to achieve remission, or for those who are dependent on steroids for symptomatic control. Intravenous tocilizumab should be started for all patients with SJIA. If there are ongoing systemic symptoms, tocilizumab should be switched to anakinra if not already used to treat macrophage activation syndrome (MAS).

Canakinumab is licensed for the treatment of SJIA and adult-onset Still's disease in patients aged two years and older who have responded inadequately to previous therapy NSAIDs and systemic corticosteroids (European Medicines Agency, 2009, updated in 2019).

[1] PICO amended following clarification with NHS England CET by email correspondence 7 December 2020. Intervention was changed from 4th line canakinumab following anakinra or tocilizumab to 4th line canakinumab following tocilizumab then anakinra if no response. Hence population was changed from SJIA refractory to or intolerant of anakinra or tocilizumab to SJIA refractory to or intolerant of tocilizumab.

2. Executive summary of the review

Three papers were included in the evidence review (Barut et al 2019, Horneff et al 2017 and Nishimura et al 2020).

Two studies were prospective case series (Horneff et al 2017 and Nishimura et al 2020) and one study was a retrospective case series (Barut et al 2019). No studies directly compared canakinumab to a control group (either placebo or active comparator).

Horneff et al 2017 was a prospective case series which included 245 patients from a national registry of systemic-onset juvenile idiopathic arthritis (SJIA) patients treated with biologics, all of whom had previously received steroids and the majority methotrexate. For those patients on interleukin-1 inhibitors (anakinra or canakinumab), the mean age of disease onset was 4.5 years (standard deviation (SD) 3.2) and the mean age of initiation of biologics was 9.6 years (SD 4.6). The paper reported results for a subgroup of seven patients who were treated with canakinumab following tocilizumab. Results for these seven patients were extracted for inclusion in the evidence review.

Nishimura et al 2020 was a prospective case series (number of centres not reported) which included 19 patients with SJIA treated with canakinumab (median age 9 years (range 1 to 19), all of whom were receiving concomitant oral corticosteroids and 47% on methotrexate (previous use of methotrexate not reported). The paper reported results separately for 15 patients who had been previously treated with tocilizumab. Results for these 15 patients were extracted for inclusion in the evidence review.

Barut et al 2019 was a single centre retrospective case series, which included 168 patients with SJIA, all of whom were treated with steroids and 75% with methotrexate. The median age of patients at time of study was 16 years (interquartile range (IQR) 9) and the median age at time of diagnosis was 5.8 years (IQR 7.2). The paper reported results for a subgroup of 27 patients treated with canakinumab, following tocilizumab in up to 18 cases and anakinra in up to 27 cases. Results for these 27 patients were extracted for inclusion in the evidence review.

Research Question 1:

1. In patients with SJIA refractory to or intolerant of anakinra or tocilizumab, what is the clinical effectiveness of canakinumab compared with current standard treatment?

Critical outcomes

The critical outcomes for decision making are quality of life, reduction and resolution of symptoms (as measured by the juvenile arthritis disease activity score (JADAS) or similar), and reduction in corticosteroid use.

The certainty of the evidence for all critical outcomes was very low when assessed using modified GRADE.

Quality of life

No evidence was identified for this outcome.

Reduction and resolution of symptoms (as measured by the juvenile arthritis disease activity score (JADAS) or similar)

Three case series (Barut et al 2019, Horneff et al 2017 and Nishimura et al 2020) provided non-comparative evidence relating to resolution and reduction of symptoms as measured by the JADAS-10 score[2], American College of Rheumatology (ACR)[3] criteria, ACR paediatric 30/50/70 criteria[4] or study's own criteria in a subgroup of SJIA patients treated with canakinumab and following tocilizumab in all or the majority of cases.

One prospective case series (Horneff et al 2017) (n=7) provided non-comparative evidence that in SJIA patients treated with canakinumab following tocilizumab, 55% of patients achieved remission when defined as JADAS-10 score of ≤1 and 43% of patients achieved remission when defined by American College of Rheumatology (ACR) criteria, at last documented follow-up response (estimated graphically; median/mean timepoint not reported). One prospective case series (Nishimura et al 2020) (n=15) provided non-comparative evidence that at 8 weeks, ACR paediatric 30, 50 and 70 criteria was achieved in all SJIA patients treated with canakinumab following tocilizumab. One single centre retrospective case series (Barut et al 2019) of 27 SJIA patients treated with canakinumab

[2] JADAS10 is a composite disease activity score (0-40) for JIA including four measures: active joint count (up to 10 joints), physician's global assessment of disease activity, parent/patient evaluation of the child's overall well-being and erythrocyte sedimentation rate (ESR).
[3] ACR preliminary criteria for remission/inactive disease includes: (i) the lowest value of the physician's judgement on global disease activity of 0 on a 100-mm visual analogue scale; (ii) erythrocyte sedimentation rate (ESR) up to 20 mm/h; (iii) C-reactive protein (CRP) up to 6 mg/l; (iv) morning stiffness lasting up to 15 min and (v) the absence of systemic manifestations (fever, rash, pericarditis, hepatomegaly, splenomegaly or lymph node swelling).
[4] Adapted ACR paediatric 30/50/70 criteria was defined as improvements of ≥30%/≥50%/≥70% from baseline in ≥3 of the six variables in JIA core set and no intermittent fever (body temperature ≤38°C) in the preceding week, with no more than one of the six variables worsening by >30%. The six JIA components were the number of joints with active arthritis, the number of joints with a limited range of motion, physician's global assessment (PGA), and patients'/parents' global assessment (PPGA) of disease activity on a 100mm visual analog scale (VAS), standardized CRP level (normal range: 0–10 mg/L), and functional ability (using the Disability Index of the Childhood Health Assessment Questionnaire, on a scale of 0–3).

following anakinra or tocilizumab[5] provided non-comparative evidence that remission[6] off medication (no usage of any anti-rheumatic drugs during the last 12 months) was achieved in three (11.5%) patients and minimal disease activity (not defined) on medication was achieved in 23 (85%) patients, all with follow-up of a minimum of 12 months (timepoint not reported).

Reduction in corticosteroid use

One prospective case series (Nishimura et al 2020) (n=15) provided non-comparative evidence that at 28 weeks, successful oral corticosteroid tapering[7] was achieved in 11 (73.3%) SJIA patients treated with canakinumab following tocilizumab, of which 10 (66.7%) were tapered and one (6.7%) was corticosteroid-free,

Important outcomes

The important outcomes for decision making are control of biochemical markers of inflammation (C-reactive protein (CRP), serum amyloid A (SAA) and erythrocyte sedimentation rate (ESR)) and changes in systemic features of disease (fever, rash, weight change and hepatosplenomegaly).

The certainty of the evidence for all important outcomes with evidence identified was very low when assessed using modified GRADE.

Control of biochemical markers of inflammation (CRP; SAA and ESR)

No evidence was identified for this outcome.

Changes in systemic features of disease (fever, rash, weight change and hepatosplenomegaly)

One prospective case series (Horneff et al 2017) (n=7) provided non-comparative evidence that 85% of SJIA patients treated with canakinumab following tocilizumab had no fever at

[5] No treatment history was provided for canakinumab treated patients. An assumption was made that these patients were treated with 4th line canakinumab following anakinra or tocilizumab based on the treatment history provided for all patients in the case series and the authors' discussion of routine treatment practice in their centre.
[6] Remission was defined as lack of fever, rash, serositis, splenomegaly, lymphadenopathy, and arthritis, as well as normal levels of erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP).
[7] Dose reduced from >0.8 mg/kg/day to ≤0.5 mg/kg/day, or from ≥0.5 mg/kg/day and ≤0.8 mg/kg/day by ≥0.3 mg/kg/day, or from any initial dose to ≤0.2 mg/kg/day, or any reduction from an initial dose of ≤0.2 mg/kg/day, while maintaining ACR paediatric 30 response.

last documented follow-up response (estimated graphically; median/mean timepoint not reported).

Research Question 2

2. In patients with SJIA refractory to or intolerant of anakinra or tocilizumab, what is the safety of canakinumab compared with current standard treatment?

The safety outcomes were adverse effects (AEs), most importantly respiratory infections, upper abdominal pain and treatment withdrawal due to adverse effects.

The certainty of the evidence for adverse effects was very low when assessed using modified GRADE.

Adverse effects

Three case series (Barut et al 2019, Horneff et al 2017 and Nishimura et al 2020) provided non-comparative evidence relating to adverse effects in a subgroup of patients treated with canakinumab following tocilizumab in all or the majority of cases. One prospective case series (Nishimura et al 2020) (n=15) reported that *"all patients experienced ≥1 AE during the study".* One prospective case series (Horneff et al 2017) (n=7) reported that *"1 patient on canakinumab treatment who had macrophage activation syndrome discontinued due to intolerance"*. One single centre retrospective case series (Barut et al 2019) (n=27) reported *that "one patient treated with canakinumab had pneumonia"*.

Research Question 3

3. In patients with SJIA refractory to or intolerant of anakinra or tocilizumab, what is the cost-effectiveness of canakinumab?

No evidence was identified on the cost effectiveness of canakinumab compared with current standard treatment.

Research Question 4

4. From the evidence selected are there any data to suggest that there are particular sub-groups of patients that would benefit from treatment with canakinumab more than others?

No evidence was identified regarding any subgroups of patients that would benefit more from treatment with canakinumab.

Limitations

The key limitation to identifying the effectiveness of canakinumab compared to standard treatment is the lack of comparative studies, with relevant results only found from 49 in scope patients within three case series (two prospective and one retrospective). Baseline characteristics and treatment history for these patients were not reported separately so it was not always possible to determine with certainty whether canakinumab was given as fourth line treatment following tocilizumab. However, this appeared likely in the majority of cases. Furthermore, it was not possible to determine follow-up timepoints in two of the case series (Barut et al 2019 and Horneff et al 2017) and one study did not use a validated disease activity measure (Barut et al 2019) for assessing remission. Many results were only reported graphically and no statistical comparisons were made with baselines, so it was not possible to determine whether the results represent statistically significant changes.

Conclusion

Very low certainty, non-comparative evidence identified for inclusion in this review is insufficient to draw conclusions about the clinical effectiveness and safety of fourth line canakinumab following current standard treatment (corticosteroids, DMARDs, and tocilizumab then anakinra) compared to standard treatment alone in patients with SJIA refractory to or intolerant of tocilizumab. The evidence is limited to 49 patients extracted from three case series and suggests that, compared to baseline, canakinumab improves disease severity, reduces concomitant corticosteroid dosage and reduces fever with few adverse effects. No results were reported for quality of life and biomarkers of inflammation (CRP, SAA and ESR). No evidence on the cost effectiveness of canakinumab compared to current standard treatments was identified. No evidence was identified for particular sub-groups of patients that would benefit more from treatment with canakinumab.

3. Methodology

Review questions

The review question(s) for this evidence review are:

1. In patients with SJIA refractory to or intolerant of anakinra or tocilizumab, what is the clinical effectiveness of canakinumab compared with current standard treatment?

2. In patients with SJIA refractory to or intolerant of anakinra or tocilizumab, what is the safety of canakinumab compared with current standard treatment?

3. In patients with SJIA refractory to or intolerant of anakinra or tocilizumab, what is the cost-effectiveness of canakinumab?

4. From the evidence selected are there any data to suggest that there are particular sub-groups of patients that would benefit from treatment with canakinumab more than others?

See Appendix A for the full review protocol.

Review process

The methodology to undertake this review is specified by NHS England in their 'Guidance on conducting evidence reviews for Specialised Services Commissioning Products' (2019).

The searches for evidence were informed by the PICO document and were conducted on 23rd October 2020.

See Appendix B for details of the search strategy.

Results from the literature searches were screened using their titles and abstracts for relevance against the criteria in the PICO framework. Full text references of potentially relevant evidence were obtained and reviewed to determine whether they met the inclusion criteria for this evidence review.

See Appendix C for evidence selection details and Appendix D for the list of studies excluded from the review and the reasons for their exclusion.

Relevant details and outcomes were extracted from the included studies and were critically appraised using a checklist appropriate to the study design. See Appendices E and F for individual study and checklist details.

The available evidence was assessed by outcome for certainty using modified GRADE. See Appendix G for GRADE Profiles.

4. Summary of included studies

Three papers were identified for inclusion (Barut et al 2019, Horneff et al 2017 and Nishimura et al 2020). Table 1 provides a summary of these included studies and full details are given in Appendix E.

Two studies were prospective case series (Horneff et al 2017 and Nishimura et al 2020) and one study was a retrospective case series (Barut et al 2019). Results were extracted for patients who were treated with canakinumab following tocilizumab in all or the majority of cases.

No cost effectiveness studies were identified.

Table 1 Summary of included studies

Study	Population	Intervention and comparison	Outcomes reported
Barut et al 2019 Retrospective case series Turkey	168 patients diagnosed with SJIA according to the International League Against Rheumatism and under 18 years of age at time of disease onset and diagnosis Only data for the 27 patients who received canakinumab were extracted for inclusion in this review No subgroups results reported for patients in scope	**Intervention** Canakinumab Median treatment duration: 19.5 months (IQR 30) Treatment received (n=168; not available for n=27 only), n (%): • Corticosteroids: 168 (100) • Methotrexate: 126 (75) • Cyclosporine A: 29 (17.3) • Anakinra: 27 (16.1) • Canakinumab: 27 (16.1) • Tocilizumab: 18 (10.7) • Etanercept: 50 (29.8) • Adalimumab: 7 (4.2)	**Critical outcomes** • Remission[8] off medication (no usage of any anti-rheumatic drugs during the last 12 months), follow-up timepoint not reported • Minimal disease activity on medication (not defined), follow-up timepoint not reported **Important outcomes** • None reported Safety • Adverse effects

[8] Remission was defined as lack of fever, rash, serositis, splenomegaly, lymphadenopathy and arthritis, as well as normal levels of erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP).

		• Intravenous immunoglobulin: 19 (11.3) Likelihood that patients were treated with 4th line canakinumab following anakinra or tocilizumab: The authors reported that: • they use tocilizumab for patients resistant to standard treatment • anakinra and canakinumab are successfully used in patients with resistant SJIA and MAS • anakinra was replaced by canakinumab in the majority of patients A maximum of 18 out of 27 (67%) canakinumab treated patients could have been previously treated with tocilizumab **Comparison** None	
Horneff et al 2017 Prospective case series Germany	245 patients on the German JIA Biologika in der Kinderrheumatologie (BIKeR) registry[9] with SJIA confirmed according to the International League of Associations of Rheumatology criteria	**Intervention details** Canakinumab No further details reported Concomitant treatment at enrolment, (n=43 IL-1 inhibitors (anakinra or canakinumab) switcher	**Critical outcomes** • Remission (JADAS10 score[10] ≤1) at last documented response • Remission (American College of Rheumatology

[9] Society for Child and Adolescent Rheumatology for Biological Therapy Registry which provides long-term prospective monitoring of the efficacy and tolerability of treatment with biologicals in patients with juvenile idiopathic arthritis in comparison with the conventional basic therapy in Germany.
[10] JADAS10 is a composite disease activity score (0-40) for JIA including four measures: active joint count (up to 10 joints), physician's global assessment of disease activity, parent/patient evaluation of the child's overall well-being and erythrocyte sedimentation rate (ESR).

	and receiving a biologic agent (etanercept, tocilizumab, anakinra and canakinumab) Only data for the 7 patients who received canakinumab following tocilizumab were extracted for inclusion in this review No subgroups results reported for patients in scope	group; not available for n=7 only), n (%): Steroids: 19 (44) Methotrexate: 18 (42) Other cDMARDs: 4 (10) Previous treatment (n=43 IL-1 inhibitors (anakinra or canakinumab) switcher group; not available for n=7 only), n (%): Steroids: 43 (100) Methotrexate: 36 (83) Other cDMARDs: 20 (47) Biologics: 39 (65) Etanercept: 32 (74) Tocilizimab: 9 (21) **Comparator details** None	(ACR) criteria[11]) at last documented response (median/mean timepoint not reported) **Important outcomes** • No fever at last documented response (median/mean timepoint not reported) **Safety** • Discontinuation of treatment due to intolerance
Nishimura et al 2020 Prospective case series Japan	Patients aged ≥2 to <20 years with a confirmed diagnosis of SJIA as per International League Against Rheumatism criteria, including active systemic features, arthritis, and CRP >30 mg/L, not receiving concomitant treatment with another biologic agent or disease-modifying drug Only data for the 15 patients who received canakinumab following	**Intervention details** Canakinumab 4 mg/kg every 4 weeks subcutaneously without any dose adjustments given following a screening period of 28 days Median duration of exposure to canakinumab was 337 days and ~65% of patients received treatment for ≥48 weeks Concomitant treatment (n=19 not available for n=15 only), n (%):	**Critical outcomes** • Achieving ACR paediatric 30 criteria[12] at 8 weeks • Achieving ACR paediatric 50 criteria[12] at 8 weeks • Achieving ACR paediatric 70 criteria[12] at 8 weeks • Successful oral corticosteroid

[11] ACR preliminary criteria for remission/inactive disease includes: (i) the lowest value of the physician's judgement on global disease activity of 0 on a 100-mm visual analogue scale; (ii) erythrocyte sedimentation rate (ESR) up to 20 mm/h; (iii) C-reactive protein (CRP) up to 6 mg/l; (iv) morning stiffness lasting up to 15 min and (v) the absence of systemic manifestations (fever, rash, pericarditis, hepatomegaly, splenomegaly or lymph node swelling).

[12] Adapted ACR paediatric 30/50/70 criteria was defined as improvements of ≥30%/≥50%/≥70% from baseline in ≥3 of the six variables in JIA core set and no intermittent fever (body temperature ≤38°C) in the preceding week, with no more than one of the six variables worsening by >30%. The six JIA components were the number of joints with active arthritis, the number of joints with a limited range of motion, physician's global assessment (PGA), and patients'/parents' global assessment (PPGA) of disease activity on a 100mm visual analog scale (VAS), standardized CRP level (normal range: 0–10 mg/L), and functional ability (using the Disability Index of the Childhood Health Assessment Questionnaire, on a scale of 0–3).

	tocilizumab were extracted for inclusion in this review No subgroups results reported for patients in scope	Oral corticosteroid: 19 (100) Methotrexate: 9 (47.4) Previous treatment (n=19 not available for n=15 only), n (%): Tacrolimus: 4 (21.1) Tocilizumab: 15 (78.9) Etanercept: 1 (5.3) **Comparator details** None	tapering[13] at 28 weeks **Important outcomes** • None reported **Safety** • Experience of ≥1 adverse event(s)
Abbreviations: ACR - American College of Rheumatology, cDMARDS – conventional disease-modifying anti-rheumatic drugs, CRP – C-reactive protein, DMARDs – disease-modifying anti-rheumatic drugs, IL – interleukin, IQR – interquartile range, JADAS – juvenile arthritis disease activity score, SJIA – systemic-onset juvenile idiopathic arthritis.			

[13] Dose reduced from >0.8 mg/kg/day to ≤0.5 mg/kg/day, or from ≥0.5 mg/kg/day and ≤0.8 mg/kg/day by ≥0.3 mg/kg/day, or from any initial dose to ≤0.2 mg/kg/day, or any reduction from an initial dose of ≤0.2 mg/kg/day, while maintaining ACR paediatric 30 response.

5. Results

In patients with SJIA refractory to or intolerant of anakinra or tocilizumab, what is the clinical effectiveness and safety of canakinumab compared with current standard treatment?

Outcome	Evidence statement
Clinical Effectiveness	
Critical outcomes	
Quality of life **Certainty of evidence:** Not applicable	Quality of life is important to patients because of the impact on the patient's function, activities of daily living and self-perceived well-being. Improvement in quality of life is a marker of successful treatment. **No evidence was identified for this outcome.**
Reduction and resolution of symptoms (as measured by the juvenile arthritis disease activity score (JADAS) or similar)	Improvement in symptoms is important to patients because this could help determine treatment choice (such as reduction of corticosteroids) and impact on the patient's function and activities of daily living. Resolution of symptoms also indicates clinical remission. Three case series (Barut et al 2019, Horneff et al 2017 and Nishimura et al 2020) provided non-comparative evidence relating to resolution and reduction of symptoms as measured by the JADAS-10 score[14], American College of Rheumatology (ACR)[15] criteria, ACR paediatric 30/50/70 criteria[16] or study's

[14] JADAS10 is a composite disease activity score (0-40) for JIA including four measures: active joint count (up to 10 joints), physician's global assessment of disease activity, parent/patient evaluation of the child's overall well-being and erythrocyte sedimentation rate (ESR).
[15] ACR preliminary criteria for remission/inactive disease includes: (i) the lowest value of the physician's judgement on global disease activity of 0 on a 100-mm visual analogue scale; (ii) erythrocyte sedimentation rate (ESR) up to 20 mm/h; (iii) C-reactive protein (CRP) up to 6 mg/l; (iv) morning stiffness lasting up to 15 min and (v) the absence of systemic manifestations (fever, rash, pericarditis, hepatomegaly, splenomegaly or lymph node swelling).
[16] Adapted ACR paediatric 30/50/70 criteria was defined as improvements of ≥30%/≥50%/≥70% from baseline in ≥3 of the six variables in JIA core set and no intermittent fever (body temperature ≤38°C) in the preceding week, with no more than

Certainty of evidence: Very low	own criteria in a subgroup of patients treated with canakinumab following tocilizumab in all or the majority of cases. Remission (defined as JADAS-10 score ≤1): • 1 prospective case series (Horneff et al 2017) of 245 patients from a national registry of SJIA patients on biologics reported results for 7 patients treated with canakinumab following tocilizumab providing non-comparative evidence that remission (defined as JADAS-10 score ≤1) was achieved in 55% of these in scope patients at last documented response (estimated from graph; median/mean timepoint not reported). (**VERY LOW)** Remission (defined by American College of Rheumatology (ACR) criteria): • 1 prospective case series (Horneff et al 2017) of 245 patients from a national registry of SJIA patients on biologics reported results for 7 patients treated with canakinumab following tocilizumab providing non-comparative evidence that remission (defined by American College of Rheumatology (ACR) criteria) was achieved in 43% of these in scope patients at last documented response (estimated from graph; median/mean timepoint not reported). (**VERY LOW)** Achieving ACR paediatric 30, 50 and 70 criteria: • 1 prospective case series (Nishimura et al 2020) of 19 SJIA patients treated with canakinumab reported results for a subgroup of 15 patients previously treated with tocilizumab providing non-comparative evidence that

one of the six variables worsening by >30%. The six JIA components were the number of joints with active arthritis, the number of joints with a limited range of motion, physician's global assessment (PGA), and patients'/parents' global assessment (PPGA) of disease activity on a 100mm visual analog scale (VAS), standardized CRP level (normal range: 0–10 mg/L), and functional ability (using the Disability Index of the Childhood Health Assessment Questionnaire, on a scale of 0–3.

	ACR paediatric 30, 50 and 70 criteria was achieved in all patients at 8 weeks. (**VERY LOW)** Remission off medication (study's criteria): • 1 single centre retrospective case series (Barut et al 2019) of 168 SJIA patients reported results for 27 patients treated with canakinumab providing non-comparative evidence that remission[17] off medication (no usage of any anti-rheumatic drugs during the last 12 months) was achieved in 3 (11.5%) patients treated with canakinumab with follow-up for a minimum of 12 months (timepoint not reported). While it is likely that canakinumab was given as 4th line treatment following tocilizumab or anakinra, only up to 67% of patients can have been previously treated with tocilizumab. (**VERY LOW)** Minimal disease activity on medication (not defined): • 1 single centre retrospective case series (Barut et al 2019) of 168 SJIA patients reported results for 27 patients treated with canakinumab providing non-comparative evidence that minimal disease activity on medication was achieved in 23 (85%) patients treated with canakinumab with follow-up of a minimum of 12 months (timepoint not reported). While it is likely that canakinumab was given as 4th line treatment following tocilizumab or anakinra, only up to 67% of patients can have been previously treated with tocilizumab. (**VERY LOW)** **These studies provided very low certainty evidence that compared to baseline, canakinumab reduces and resolves symptoms in patients with SJIA refractory to or intolerant of tocilizumab.**

[17] Remission was defined as lack of fever, rash, serositis, splenomegaly, lymphadenopathy, and arthritis, as well as normal levels of erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP).

Reduction in corticosteroid use **Certainty of evidence:** Very low	Assessment of corticosteroid use is important to patients because long-term steroid use can be harmful and cause side effects unwanted by patients and may affect treatment choice. One prospective case series (Nishimura et al 2020) provided non-comparative evidence relating to reduction in corticosteroid use in a subgroup of patients treated with canakinumab following tocilizumab. Successful oral corticosteroid tapering: • 1 prospective case series (Nishimura et al 2020) of 19 SJIA patients treated with canakinumab reported results for a subgroup of 15 patients previously treated with tocilizumab providing non-comparative evidence that successful oral corticosteroid tapering[18] was achieved at 28 weeks in 11 (73.3%) of these in scope patients, of which 10 (66.7%) were tapered and 1 (6.7%) was corticosteroid-free. **(VERY LOW)** **This study provided very low certainty evidence that compared to baseline, canakinumab reduces corticosteroid use up to 28 weeks in patients with SJIA refractory to or intolerant of tocilizumab.**
Important outcomes	
Control of biochemical markers of inflammation (C-reactive protein (CRP), serum amyloid A (SAA) and erythrocyte	Assessment of inflammatory biomarkers is important to patients because these blood tests are a direct, quantifiable measure of disease activity and treatment response. Return to normal levels can indicate biochemical remission. **No evidence was identified for this outcome.**

[18] Dose reduced from >0.8 mg/kg/day to ≤0.5 mg/kg/day, or from ≥0.5 mg/kg/day and ≤0.8 mg/kg/day by ≥0.3 mg/kg/day, or from any initial dose to ≤0.2 mg/kg/day, or any reduction from an initial dose of ≤0.2 mg/kg/day, while maintaining ACR paediatric 30 response.

sedimentation rate (ESR)) **Certainty of evidence:** Not applicable	
Changes in systemic features of disease (fever, rash, weight change and hepatosplenomegaly) **Certainty of evidence:** Very low	Assessment of systemic disease is important to patients because this could help determine treatment choice and because of the impact on the patient's self-perceived well-being. One prospective case series (Horneff et al 2017) provided non-comparative evidence relating to changes in systemic features of disease in a subgroup of patients treated with canakinumab following tocilizumab. • 1 prospective case series (Horneff et al 2017) of 245 patients from a national registry of SJIA patients on biologics reported results for 7 patients treated with canakinumab following tocilizumab providing non-comparative evidence that 85% of patients had no fever at last documented response (estimated from graph; median/mean timepoint not reported). **(VERY LOW)** **This study provided very low certainty evidence that compared to baseline, canakinumab improves systemic features of disease in patients with SJIA refractory to or intolerant of tocilizumab.**
Safety	
Adverse effects **Certainty of evidence:** Very low	Safety outcomes are relevant to patients because adverse events can affect survival, quality of life, tolerability and overall responses. Three case series (Barut et al 2019, Horneff et al 2017 and Nishimura et al 2020) provided non-comparative evidence

	relating to adverse effects in a subgroup of patients treated with canakinumab following tocilizumab. Severe adverse effects: • 1 single centre retrospective case series (Barut et al 2019) of 168 SJIA patients reported results for a subgroup of 27 patients treated with canakinumab providing non-comparative evidence *that "one patient treated with canakinumab had pneumonia"*. While it is likely that canakinumab was given as 4th line treatment following tocilizumab or anakinra, only up to 67% can have been previously treated with tocilizumab. (**VERY LOW)** Experience ≥1 adverse event(s) during the study: • 1 prospective case series (Nishimura et al 2020) of 19 SJIA patients treated with canakinumab reported results for a subgroup of 15 patients previously treated with tocilizumab providing non-comparative evidence that *"all patients experienced ≥1 AE during the study".* **(VERY LOW)** Discontinuation of medication due to intolerance: • 1 prospective case series (Horneff et al 2017) of 245 patients from a national registry of SJIA patients on biologics reported results for 7 patients treated with canakinumab following tocilizumab providing non-comparative evidence that *"1 patient on canakinumab treatment who had MAS discontinued due to intolerance"*. (**VERY LOW)** **This study provided very low certainty evidence on the safety of canakinumab in patients with SJIA refractory to or intolerant of tocilizumab.**

Abbreviations: ACR – American College of Rheumatology, AE – adverse event, JADAS – juvenile arthritis disease activity score, MAS – macrophage activation syndrome, SJIA – systemic-onset juvenile idiopathic arthritis.

From the evidence selected are there any data to suggest that there are particular sub-groups of patients that would benefit from treatment with canakinumab more than others?

Outcome	Evidence statement
Subgroups	No evidence was identified regarding any subgroups of patients that would benefit more from treatment with canakinumab in patients with SJIA refractory to or intolerant of tocilizumab.

In patients with SJIA refractory to or intolerant of anakinra or tocilizumab, what is the cost-effectiveness of canakinumab?

Outcome	Evidence statement
Cost Effectiveness	No evidence was identified for cost effectiveness

6. Discussion

This rapid evidence review considered the evidence for the clinical effectiveness and safety of fourth line canakinumab following current standard treatment (corticosteroids, DMARDs, and tocilizumab then anakinra) compared with standard treatment alone in patients with SJIA refractory to or intolerant of tocilizumab. The critical outcomes of interest were improvement in quality of life, reduction and resolution of symptoms (as measured by the JADAS or similar), and reduction in corticosteroid use. The important outcomes of interest were control of biochemical markers of inflammation (CRP, SAA and ESR) and changes in systemic features of disease (fever, rash, weight change and hepatosplenomegaly).

No comparative studies were found that met the inclusion criteria for population and intervention. To be in scope patients with SJIA needed to be treated with canakinumab as fourth line treatment following first line treatment with corticosteroids, second line treatment with a conventional DMARD (methotrexate) and third line treatment with tocilizumab then anakinra if no response.[19] Limited evidence was available with only results from 49 in scope patients extracted from three case series (Barut et al 2019, Horneff et al 2017 and Nishimura et al 2020), only one of which was specifically designed to assess the effectiveness of canakinumab (Nishimura et al 2020). Results from the 49 canakinumab treated SJIA patients provided limited evidence for reduction and resolution of symptoms (as measured by JADAS or similar) and reduction in corticosteroid use (critical outcomes), changes in fever, rash and hepatosplenomegaly (important outcomes), and safety outcomes. No evidence was available for the other outcomes of interest. The case series were at very high risk of bias mainly due to limitations in the reporting of baseline characteristics and results for the patient subgroup of interest. Certainty in the evidence for critical and important outcomes was very low when assessed using modified GRADE.

Horneff et al 2017 was a prospective case series of 245 patients included in a national registry of SJIA patients treated with biologics, seven of which were treated with canakinumab following tocilizumab. Relevant outcomes for these seven patients were extracted for inclusion in this review. Baseline demographic and clinical characteristics were not reported separately for the patients who received canakinumab following tocilizumab. It is likely that canakinumab was given as fourth line treatment in these

[19] PICO amended following clarification with NHS England CET by email correspondence 7 December 2020. Intervention was changed from 4th line canakinumab following anakinra or tocilizumab to 4th line canakinumab following tocilizumab then anakinra if no response. Hence population was changed from SJIA refractory to or intolerant of anakinra or tocilizumab to SJIA refractory to or intolerant of tocilizumab.

patients, as all patients in the study had previously received steroids and the majority of patients had previously received or were on concomitant methotrexate. Patients were followed-up as part of the registry at three and six months after starting biologics and six monthly thereafter, and results were reported up to 24 months and at last documented response timepoint. Results for in scope patients were only reported graphically for remission and no fever, and only for the last documented observation timepoint (no mean/median length of follow-up reported).

Nishimura et al 2020 was a prospective case series (number of centres not reported) which included 19 patients with SJIA treated with canakinumab with up to 48 weeks follow-up. The paper reported results separately for 15 patients who had been previously treated with tocilizumab. Results for this group were extracted for inclusion in the evidence review. Baseline demographic and clinical characteristics were not reported separately for patients who received prior tocilizumab. It is not known for certain whether canakinumab was given as fourth line treatment in these patients, as although it was reported that all patients were on concomitant oral corticosteroids, previous use of methotrexate was not reported, only that just under half were receiving methotrexate at time of study. One patient previously treated with tocilizumab was discontinued from the study before eight weeks either due to adverse events or loss of efficacy.

Barut et al 2019 was a single centre retrospective case series, which included 168 patients with SJIA. The paper reported results for a subgroup of 27 patients treated with canakinumab. Results for these 27 patients were extracted for inclusion in the evidence review. Baseline demographic and clinical characteristics were not reported separately for these canakinumab treated patients. It was not possible to determine whether canakinumab was given as fourth line treatment in these patients, only that all 168 patients were treated with steroids, 75% with methotrexate, 17% with cyclosporine A, 16% with anakinra and 11% with tocilizumab. However, it seems likely that canakinumab was given as fourth line treatment following tocilizumab or anakinra as the authors reported that they use tocilizumab for patients resistant to standard treatment; anakinra and canakinumab are successfully used in patients with resistant SJIA and macrophage activation syndrome; and anakinra was replaced by canakinumab in the majority of patients. It should be noted however, that only 18 patients out of 168 patients were reported to be treated with tocilizumab, and therefore it is only possible that a maximum of 18 out of 27 (67%) canakinumab treated patient were previously treated with tocilizumab. The median treatment duration of canakinumab was reported to be 19.5 months but the length of retrospective follow-up was not reported. Furthermore, a validated disease activity measure was not used to assess remission and no definition was provided for minimal

disease activity. The results for adverse effects were inconsistent with the authors reporting that one patient treated with canakinumab had pneumonia in the discussion, but not in the results section.

For all included studies, no statistical comparisons were made with baseline, so it was not possible to determine whether the results represent statistically significant changes.

7. Conclusion

The evidence included in this review is insufficient to draw conclusions about the clinical effectiveness and safety of fourth line canakinumab following current standard treatment (corticosteroids, DMARDs, and tocilizumab then anakinra) compared to standard treatment alone in patients with SJIA refractory to or intolerant of tocilizumab. The key limitation to identifying the effectiveness of canakinumab compared to standard treatment is the lack of comparative studies with only relevant results found from sub-groups of in scope patients within case series.

Limited evidence was identified with results for only 49 patients treated with canakinumab extracted from two prospective case series and one retrospective case series. Baseline characteristics and treatment history for these patients were not reported separately, so although it appears highly likely that canakinumab was given as fourth line treatment following tocilizumab in the majority of cases, this was not always certain.

This very low certainty, non-comparative evidence for 49 patients with SJIA refractory to or intolerant of tocilizumab suggests that canakinumab improves disease severity, reduces concomitant corticosteroid dosage and reduces fever with few adverse effects. No results were reported for quality of life and biomarkers of inflammation (CRP, SAA and ESR).

No evidence on the cost effectiveness of canakinumab compared to current standard treatments was identified.

No evidence was identified for particular sub-groups of patients that would benefit more from treatment with canakinumab.

Appendix A PICO Document

The review questions for this evidence review are:

1. In patients with SJIA refractory to or intolerant of anakinra or tocilizumab, what is the clinical effectiveness of canakinumab compared with current standard treatment?

2. In patients with SJIA refractory to or intolerant of anakinra or tocilizumab, what is the safety of canakinumab compared with current standard treatment?

3. In patients with SJIA refractory to or intolerant of anakinra or tocilizumab, what is the cost-effectiveness of canakinumab?

4. From the evidence selected are there any data to suggest that there are particular sub-groups of patients that would benefit from treatment with canakinumab more than others?

P – Population and Indication	Patients with a diagnosis of systemic-onset juvenile idiopathic arthritis (SJIA) that are refractory or intolerant to anakinra or tocilizumab. *SJIA is a severe subtype of juvenile idiopathic arthritis (JIA) characterised by arthritis with systemic inflammation that can cause hepatosplenomegaly, lymphadenopathy and serositis. Some patients with SJIA show a monophasic course, with resolution of all symptoms and no recurrences, but the majority develop recurring symptoms.*
I – Intervention	Canakinumab as 4th line treatment, after: 1. Corticosteroids 2. DMARDs (methotrexate)[20] 3. Tocilizumab then anakinra if no response[20] *Canakinumab is a recombinant human monoclonal antibody that is proposed as a 4th line treatment option for patients with SJIA that is refractory to the three lines of current standard treatment.*
C – Comparator(s)	No treatment with canakinumab as 4th line treatment after all the following:

[20] PICO amended following clarification with NHS England CET by email correspondence 7 December 2020.

	1. Corticosteroids 2. DMARDs (methotrexate)[20] 3. Tocilizumab then anakinra if no response[20] *Current standard treatment for SJIA involves three lines of treatment. First line treatment is with corticosteroids, followed if necessary by treatment with a disease-modifying antirheumatic drug (DMARD). If remission is still not achieved, third line treatment is with tocilizumab and/or anakinra.*
O – Outcomes	*Response to treatment for all of the clinical effectiveness outcomes would be expected to be achieved within 12 weeks of starting treatment. There are no known standard MCIDs for any of the outcome measures with SJIA.* **<u>Clinical Effectiveness</u>** *<u>Critical to decision-making:</u>* • Quality of life: preferred measure is the Child Health Assessment Questionnaire (CHAQ) or similar. *This questionnaire assesses quality of life specific to children with juvenile rheumatoid arthritis by measuring disability, discomfort and pain.* *Quality of life is important to patients because of the impact on the patient's function, activities of daily living and self-perceived well-being. Improvement in quality of life is a marker of successful treatment.* • Reduction and resolution of symptoms (as measured by the juvenile arthritis disease activity score (JADAS) or similar). *Improvement in symptoms is important to patients because this could help determine treatment choice (such as reduction of corticosteroids) and impact on the patient's function and activities of daily living. Resolution of symptoms also indicates clinical remission.* • Reduction in corticosteroid use *Assessment of corticosteroid use is important to patients because long-term steroid use can be*

	harmful and cause side-effects unwanted by patients and may affect treatment choice. *These are considered the outcomes most critical to decision making as they include the patient's perspective on their condition. They help to determine if the treatment is effective at reducing symptoms, modifying disease activity, improving quality of life and improving biochemical markers.* *<u>Important to decision-making:</u>* • Control of biochemical markers of inflammation (C-reactive protein; CRP, serum amyloid A; SAA and erythrocyte sedimentation rate; ESR). *Assessment of inflammatory biomarkers is important to patients because these blood tests are a direct, quantifiable measure of disease activity and treatment response. Return to normal levels can indicate biochemical remission.* • Changes in systemic features of disease (fever, rash, weight change and hepatosplenomegaly) *Assessment of systemic disease is important to patients because this could help determine treatment choice and because of the impact on the patient's self-perceived well-being* **<u>Safety</u>** • Adverse effects – most important are respiratory infections, upper abdominal pain and treatment withdrawal due to adverse effects **<u>Cost effectiveness</u>**
Inclusion criteria	
Study design	Systematic reviews, randomised controlled trials, controlled clinical trials, cohort studies. If no higher level quality evidence is found, case series can be considered.
Language	English only
Patients	Human studies only

Age	All ages
Date limits	2010-2020
Exclusion criteria	
Publication type	Conference abstracts, non-systematic reviews, narrative reviews, commentaries, letters, editorials, prepublication prints and guidelines
Study design	Case reports, resource utilisation studies

Appendix B Search strategy

Medline, Embase, Cochrane Library and PubMed were searched limiting the search to papers published in English language in the last 10 years. Conference abstracts, commentaries, letters, editorials and case reports were excluded.

Search dates: 1 January 2010 to 23 October 2020

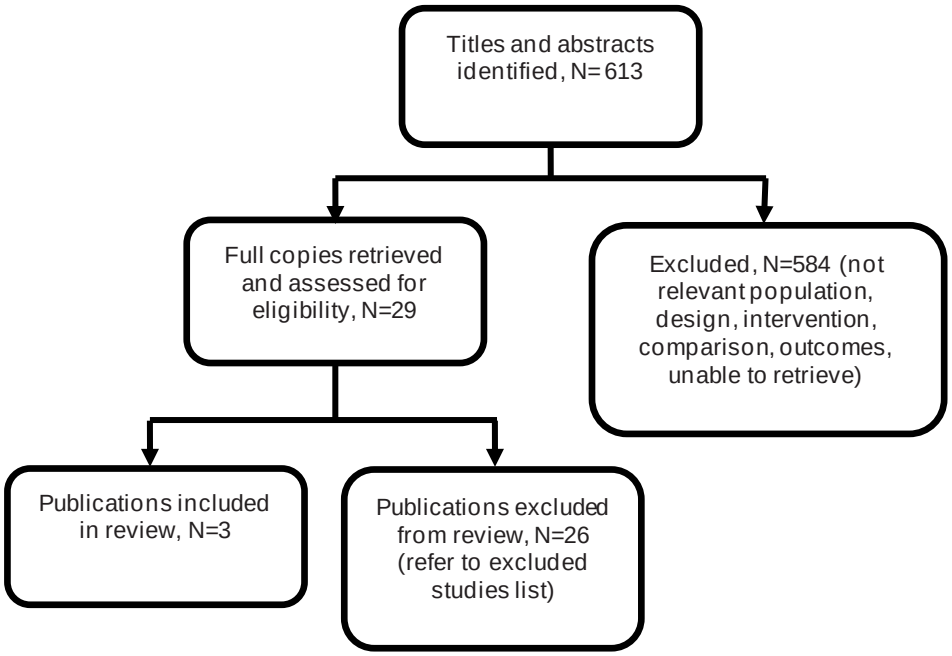
Medline search

# ▲	Searches
1	((juvenile adj3 arthritis) or sjia or jia).ti,ab,kw.
2	((still* adj2 disease) or aosd).ti,ab,kw.
3	Still's Disease, Adult-Onset/ or Arthritis, Juvenile/
4	1 or 2 or 3
5	(canakinumab or ilaris).mp.
6	4 and 5
7	exp "Drug-Related Side Effects and Adverse Reactions"/
8	Adverse Drug Reaction Reporting Systems/
9	(ae or co or de).fs. or safe.ti,ab. or safety.ti,ab. or side-effect*.ti,ab. or undesirable effect*.ti,ab. or treatment emergent.ti,ab. or tolerability.ti,ab. or toxicity.ti,ab. or adrs.mp. or (adverse adj2 (effect or effects or reaction or reactions or event or events or outcome or outcomes)).ti,ab.
10	Substance Withdrawal Syndrome/
11	Abdominal Pain/
12	exp Respiratory Tract Infections/
13	((drug or treatment or therap* or substance) adj2 withdraw*).ti,ab,kw.
14	(abdom* adj2 pain).ti,ab,kw.
15	((respirat* adj3 infection*) or urti or lrti or pneumonia).ti,ab,kw.
16	7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15
17	5 and 16
18	6 or 17
19	(comment or editorial or letter or review).pt. or case report.ti.
20	18 not 19
21	limit 20 to ("systematic review" or "reviews (maximizes specificity)")
22	20 or 21
23	limit 22 to (english language and yr="2010 -Current")
24	exp animals/ not humans/
25	23 not 24

Appendix C Evidence selection

The literature searches identified 613 references. These were screened using their titles and abstracts and 29 references were obtained in full text and assessed for relevance. Of these, 3 references are included in the evidence summary. The remaining 26 references were excluded and are listed in Appendix D.

Figure 1- Study selection flow diagram



References submitted with Preliminary Policy Proposal

None submitted

Appendix D Excluded studies table

Study reference	Reason for exclusion
Aygun D, Sahin S, Adrovic A, Barut K, Cokugras H, Camcioglu Y, et al. The frequency of infections in patients with juvenile idiopathic arthritis on biologic agents: 1-year prospective study. Clinical Rheumatology. 2019;38(4):1025-30.	No results for SJIA patients treated with CAN. Not possible to determine if CAN given 4th line in these patients
Baris HE, Anderson E, Sozeri B, Dedeoglu F. Impact of biologics on disease course in systemic onset juvenile idiopathic arthritis. Clinical Rheumatology. 2018;37(12):3263-73.	No results specifically for 4th line CAN for SJIA
Barut K, Yucel G, Sinoplu AB, Sahin S, Adrovic A, Kasapcopur O. Evaluation of macrophage activation syndrome associated with systemic juvenile idiopathic arthritis: single center experience over a one-year period. Turk Pediatri Arsivi. 2015;50(4):206-10.	Paper reported in Turkish
Brunner HI, Quartier P, Alexeeva E, Constantin T, Kone-Paut I, Marzan K, et al. Efficacy and Safety of Canakinumab in sJIA Patients with and without Fever at Baseline: Results from an Open-label, Active Treatment Extension Study. Arthritis & Rheumatology. 2020;10:10.	No results specifically for SJIA patients who had CAN 4th line after TOC
Cabrera N, Avila-Pedretti G, Belot A, Larbre JP, Mainbourg S, Duquesne A, et al. The benefit-risk balance for biological agents in juvenile idiopathic arthritis: a meta-analysis of randomized clinical trials. Rheumatology. 2020;59(9):2226-36.	Systematic review looking at biological agents in juvenile idiopathic arthritis. Includes results for CAN in SJIA but these are taken from 1 study (Ruperto 2012 phase 3 studies which are out of scope)
Cakan M, Karadag SG, Ayaz NA. Canakinumab in colchicine resistant familial Mediterranean fever and other pediatric rheumatic diseases. Turkish Journal of Pediatrics. 2020;62(2):167-74.	Includes 2 SJIA patients treated with CAN but not possible to determine whether CAN was given as 4th line treatment

Dumaine C, Bekkar S, Belot A, Cabrera N, Malik S, von Scheven A, et al. Infectious adverse events in children with Juvenile Idiopathic Arthritis treated with Biological Agents in a real-life setting: Data from the JIRcohorte. Joint, Bone, Spine: Revue du Rhumatisme. 2020;87(1):49-55.	No separate results reported for SJIA patients on CAN
Feist E, Quartier P, Fautrel B, Schneider R, Sfriso P, Efthimiou P, et al. Efficacy and safety of canakinumab in patients with Still's disease: exposure-response analysis of pooled systemic juvenile idiopathic arthritis data by age groups. Clinical & Experimental Rheumatology. 2018;36(4):668-75.	No results specifically for SJIA patients who had CAN 4th line after TOC
Grom AA, Ilowite NT, Pascual V, Brunner HI, Martini A, Lovell D, et al. Rate and Clinical Presentation of Macrophage Activation Syndrome in Patients With Systemic Juvenile Idiopathic Arthritis Treated With Canakinumab. Arthritis & Rheumatology. 2016;68(1):218-28.	The study reviews cases of MAS in CAN treated SJIA patients identified from Ruperto 2012 phase 2 & 3 trials. Of the 19 patients identified, none were on 4th line CAN treatment
Hinze C, Fuehner S, Kessel C, Wittkowski H, Lainka E, Baehr M, et al. Impact of IL1RN Variants on Response to Interleukin-1 Blocking Therapy in Systemic Juvenile Idiopathic Arthritis. Arthritis & Rheumatology. 2020;72(3):499-505.	No results specifically for 11 SJIA patients who had CAN after TOC. Previous treatments not reported separately for CAN patients
Klein A, Klotsche J, Hugle B, Minden K, Hospach A, Weller-Heinemann F, et al. Long-term surveillance of biologic therapies in systemic-onset juvenile idiopathic arthritis: data from the German BIKER registry. Rheumatology. 2020;59(9):2287-98.	No results specifically for SJIA patients who had CAN 4th line (+ mean number of 2.1 bDMARDs indicated that CAN is 4th or 5th line but bDMARDs might or might not include TOC)
McHugh J. Long-term safety of canakinumab in systemic JIA. Nature Reviews Rheumatology. 2018;14(11):622.	Commentary on Ruperto 2018 (out of scope)

Minden K, Horneff G, Niewerth M, Seipelt E, Aringer M, Aries P, et al. Time of disease-modifying antirheumatic drug start in juvenile idiopathic arthritis and the likelihood of a drug-free remission in young adulthood. Arthritis Care and Research. 2019;71(4):471-81.	No separate results reported for SJIA patients on CAN
Niehues T, Ozgur TT. The Efficacy and Evidence-Based Use of Biologics in Children and Adolescents: Using Monoclonal Antibodies and Fusion Proteins as Treatments. Deutsches Arzteblatt International. 2019;116(42):703-10.	SR of clinical trials and guidelines on therapeutic monoclonal antibodies and fusion proteins approved for paediatric use. Includes one study (Ruperto 2012 phase 3 studies which are out of scope) for CAN in SJIA
Otten MH, Anink J, Spronk S, van Suijlekom-Smit LW. Efficacy of biological agents in juvenile idiopathic arthritis: a systematic review using indirect comparisons. Ann Rheum Dis. 2013;72(11):1806-12.	No meta-analysis of results specifically for in-scope patients who had CAN 4th line. Review individual studies individually for inclusion/exclusion
Quartier P, Alexeeva E, Tamas C, Chasnyk V, Wulffraat N, Palmblad K, et al. Tapering Canakinumab Monotherapy in Patients with Systemic Juvenile Idiopathic Arthritis in Clinical Remission: Results from an Open-label, Randomized Phase IIIb/IV Study. Arthritis & Rheumatology. 2020;11:11.	No results specifically for SJIA patients who had CAN 4th line after TOC
Rossi-Semerano L, Fautrel B, Wendling D, Hachulla E, Galeotti C, Semerano L, et al. Tolerance and efficacy of off-label anti-interleukin-1 treatments in France: a nationwide survey. Orphanet Journal Of Rare Diseases. 2015;10:19.	Only 2 patients are in scope. Results are available for clinical response only not disease activity score. 3 other case series identified for inclusion which report larger numbers of patients Barut 2019 (n=27) Horneff 2017 (n=7) Nishimura 2020 (n=15)
Ruperto N, Brunner HI, Quartier P, Constantin T, Wulffraat N, Horneff G, et al. Two randomized trials of canakinumab in systemic juvenile idiopathic arthritis. New England Journal of Medicine. 2012;367(25):2396-406.	No results for specific in-scope patients who had canakinumab 4th line after TOC (up to 42% population had either ANA or TOC therefore at least 58% (majority) did not have ANA or TOC before CAN)

Ruperto N, Brunner HI, Quartier P, Constantin T, Wulffraat NM, Horneff G, et al. Canakinumab in patients with systemic juvenile idiopathic arthritis and active systemic features: results from the 5-year long-term extension of the phase III pivotal trials. Annals of the Rheumatic Diseases. 2018;77(12):1710-9.	Long term extension study of Ruperto 2012 phase 3 trials (out of scope). 144 patients entered the extension trial. Ruperto 2012 (ref#20) excluded as no results for in-scope patients who had CAN 4th line after TOC (up to 42% population had either ANA or TOC therefore at least 58% (majority) did not have ANA or TOC before CAN)
Ruperto N, Quartier P, Wulffraat N, Woo P, Ravelli A, Mouy R, et al. A phase II, multicenter, open-label study evaluating dosing and preliminary safety and efficacy of canakinumab in systemic juvenile idiopathic arthritis with active systemic features. Arthritis & Rheumatism. 2012;64(2):557-67.	Study does not include any patients treated with CAN who were previously treated with TOC.
Schulert GS, Minoia F, Bohnsack J, Cron RQ, Hashad S, Kon EPI, et al. Effect of Biologic Therapy on Clinical and Laboratory Features of Macrophage Activation Syndrome Associated With Systemic Juvenile Idiopathic Arthritis. Arthritis care & research. 2018;70(3):409-19.	No meta-analysis of results specifically for in-scope patients who had CAN 4th line. Review individual studies individually for inclusion/exclusion
Shenoi S, Horneff G, Cidon M, Ramanan AV, Kimura Y, Quartier P, et al. The burden of systemic juvenile idiopathic arthritis for patients and caregivers: an international survey and retrospective chart review. Clinical & Experimental Rheumatology. 2018;36(5):920-8.	Not clear how many or if any patients who were treated with CAN had already been treated with TOC. No results reported specifically for 4th line CAN for SJIA
Sota J, Insalaco A, Cimaz R, Alessio M, Cattalini M, Gallizzi R, et al. Drug Retention Rate and Predictive Factors of Drug Survival for Interleukin-1 Inhibitors in Systemic Juvenile Idiopathic Arthritis. Frontiers in Pharmacology. 2018;9:1526.	No results for in-scope patients who had canakinumab 4th line after TOC
Sota J, Vitale A, Insalaco A, Sfriso P, Lopalco G, Emmi G, et al. Safety profile of the interleukin-1 inhibitors anakinra and canakinumab in real-life clinical practice: a nationwide multicenter retrospective observational study. Clinical Rheumatology. 2018;37(8):2233-40.	No results specifically for 4th line CAN for SJIA

Tarp S, Amarilyo G, Foeldvari I, Christensen R, Woo JM, Cohen N, et al. Efficacy and safety of biological agents for systemic juvenile idiopathic arthritis: a systematic review and meta-analysis of randomized trials. Rheumatology (Oxford). 2016;55(4):669-79.	No meta-analysis of results specifically for in-scope patients who had CAN 4th line. Review individual studies individually for inclusion/exclusion
Woerner A, Uettwiller F, Melki I, Mouy R, Wouters C, Bader-Meunier B, et al. Biological treatment in systemic juvenile idiopathic arthritis: achievement of inactive disease or clinical remission on a first, second or third biological agent. RMD Open. 2015;1(1):e000036.	Study includes 4 patients who had ANA followed by CAN and no further treatment plus 1 patient who had ANA followed by TOC followed by CAN. Very limited results reported for these patients with only a statement on whether they achieved inactive disease or clinical remission but no disease active scores are reported and therefore it is to be excluded
Abbreviations: ANA – anakinra, bDMARDs – biologic disease-modifying anti-rheumatic drugs, CAN – canakinumab, MAS – macrophage activation syndrome, SJIA – systemic juvenile idiopathic arthritis, TOC – tocilizumab.	

Appendix E Evidence Table

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
Barut K, Adrovic A, Sahin S, Tarcin G, Tahaoglu G, Koker O, et al. Prognosis, complications and treatment response in systemic juvenile idiopathic arthritis patients: A single-center experience. International Journal of Rheumatic Diseases. 2019;22(9):1661-9. **Study location** Turkey (1 paediatric rheumatology outpatient department) **Study type** Retrospective case series **Study aim** To investigate demographic and clinical features, long-term treatment response and disease complications in a large SJIA cohort **Study dates**	**Inclusion criteria** Patients diagnosed with SJIA according to the International League Against Rheumatism criteria and under 18 years of age at time of disease onset and time of diagnosis **Exclusion criteria** Patients with juvenile idiopathic arthritis subtypes other than SJIA; follow-up shorter than 12 months; history of psoriasis; underlying other inflammatory conditions (such as familial Mediterranean fever and inflammatory bowel disease); presence of immunoglobin M rheumatoid factor on at least 2 occasions for at least 3 months **Sample size** n=27 in scope patients The study included 168 SJIA patients (total sample size). Relevant outcomes for the 27	**Intervention details** n=27 Canakinumab Median treatment duration: 19.5 months (IQR 30) **Comparator details** None	**Critical outcomes** **Reduction and resolution of symptoms (as measured by the juvenile arthritis disease activity score (JADAS) or similar)** • **Remission[21] off medication (no usage of any anti-rheumatic drugs during the last 12 months), n (%)** Follow-up time point not reported (n=27): 3 (11.5) • **Minimal disease activity on medication (not defined), n (%)** Follow-up time point not reported (n=27): 23 (85) **Important outcomes** None reported **Safety**	This study was appraised using the Joanna Briggs Institute 2017 Critical Appraisal Checklist for Case Series. The appraisal was conducted in relation to the patients within this study who received canakinumab 1. YES 2. YES 3. YES 4. YES 5. YES 6. NO 7. NO 8. NO 9. YES 10. NO **Other comments** This was a retrospective case series which included 168 patients with SJIA, 27 (16%) of which were treated with canakinumab and included in this review.

[21] Remission (no disease activity) was defined as lack of fever, rash, serositis, splenomegaly, lymphadenopathy, and arthritis, as well as normal levels of erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP).

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
January 2003 to December 2017	patients who were treated with canakinumab were extracted for inclusion in this review. **Baseline characteristics** (n=27) Not reported All patients (n=168) • Female/male 87/81 (51.8%/48.2%) • Median age at time of study: 16 years (IQR 9) • Median age at time of diagnosis: 5.8 years (IQR 7.2) • Disease course: o Monocyclic: 53 (31.5%) o Polycyclic: 23 (13.7%) o Persistent: 92 (54.8%) Treatment received, n (%), and duration, median (IQR): • Corticosteroids: 168 (100) for 12 months (43.5) • Methotrexate: 126 (75) for 27 months (53.8) • Cyclosporine A: 29 (17.3) for 8 months (16) • Anakinra: 27 (16.1) for 3 months (8) • Canakinumab: 27 (16.1) for 19.5 months (30) • Tocilizumab: 18 (10.7) for 7 months (31)		One patient treated with canakinumab had pneumonia	No baseline demographics and clinical characteristics were reported for the canakinumab treated patients. Previous treatments were not reported for the canakinumab treated patients, so it is not clear if canakinumab was given as 4th line treatment following tocilizumab or anakinra. However, this seems likely given that all patients were treated with steroids, 75% of all patients were treated with methotrexate, 17% with cyclosporine A, 16% with anakinra and 11% with tocilizumab. Furthermore, the authors reported that they use tocilizumab for patients resistant to standard treatment, anakinra and canakinumab are successfully used in patients with resistant SJIA and macrophage activation syndrome, and anakinra was replaced by canakinumab in the majority of patients. However, given that only 18 patients out of 168 patients were reported to be treated with tocilizumab, it is only possible that a maximum of 18 out of 27 (67%) canakinumab treated patient were previously treated with

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
	• Etanercept: 50 (29.8) for 25 months (49.8) • Adalimumab: 7 (4.2) for 6 months (11.7) • Intravenous immunoglobulin: 19 (11.3), no duration reported			tocilizumab in line with the PICO. A validated disease activity measure was not used to assess remission and no definition is provided for minimal disease activity. No comparisons were made between follow-up and baseline results. In the discussion, the authors reported that one patient treated with canakinumab had pneumonia, but this is inconsistent with the adverse events reported in the results section with no adverse events reported for canakinumab treated patients. The authors were contacted for clarification, but no response was received. **Source of funding** Not reported
Horneff G, Schulz AC, Klotsche J, Hospach A, Minden K, Foeldvari I, et al. Experience with etanercept, tocilizumab and interleukin-1 inhibitors in systemic onset juvenile	**Inclusion criteria** Patients in the German JIA Biologika in der Kinderrheumatologie (BIKeR) registry[22] with SJIA confirmed according to the International	**Intervention details** Canakinumab No further details given **Comparator details** None	**Critical outcomes** **Reduction and resolution of symptoms (as measured by the juvenile arthritis disease activity score (JADAS) or similar)**	This study was appraised using the Joanna Briggs Institute 2017 Critical Appraisal Checklist for Case Series. The appraisal was conducted in relation to the patients within

[22] Society for Child and Adolescent Rheumatology for Biological Therapy Registry which provides long-term prospective monitoring of the efficacy and tolerability of treatment with biologicals in patients with juvenile idiopathic arthritis in comparison with the conventional basic therapy in Germany.

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
idiopathic arthritis patients from the BIKER registry. Arthritis Research & Therapy. 2017;19(1):256. **Study location** Germany **Study type** Prospective case series (national registry) **Study aim** To analyse the experience with several biologic treatments in patients with SJIA in clinical practice **Study dates** 2000 to 2015	League of Associations of Rheumatology (ILAR) criteria and who were starting treatment with a biologic agent (etanercept, tocilizumab, anakinra and canakinumab) and had assessments at baseline and at least one follow-up visit **Exclusion criteria** None reported **Sample size** n=7 in scope patients The study included 245 SJIA patients exposed to a biologic agent (total sample size), 22 of whom were treated with canakinumab and 7 of whom received tocilizumab prior to canakinumab. Relevant outcomes for the 7 canakinumab treated patients with prior tocilizumab use were extracted for inclusion in this review. **Baseline characteristics** (n=7) Not reported		• **Remission (JADAS-10[23] score ≤1)** Last documented response, no further details given (n=7): 55% of patients (taken from graph) • **Remission (American College of Rheumatology (ACR) criteria[24])** Last documented response, no further details given (n=7): 43% of patients (taken from graph) **Important outcomes** **Changes in systemic features of disease (fever, rash, weight change and hepatosplenomegaly)** **No fever** Last documented response, no further details given (n=7): 85% of patients (taken from graph) **Safety**	this study who received canakinumab and prior tocilizumab 1. YES 2. YES 3. YES 4. YES 5. UNCLEAR 6. NO 7. NO 8. NO 9. YES 10. NO **Other comments** This was a long-term prospective case series of 245 SJIA patients included in a national registry of SJIA patients on biologics. The series included 7 patients on canakinumab who had been previously treated with tocilizumab and these patients have been included in this review. Patients were only included in the analyses if they had assessments at baseline and at least one follow up visit (after 3 and 6 months, and 6

[23] JADAS10 is a composite disease activity score (0-40) for JIA including four measures: active joint count (up to 10 joints), physician's global assessment of disease activity, parent/patient evaluation of the child's overall well-being and erythrocyte sedimentation rate (ESR).
[24] ACR preliminary criteria for remission/inactive disease includes: (i) the lowest value of the physician's judgement on global disease activity of 0 on a 100-mm visual analogue scale; (ii) erythrocyte sedimentation rate (ESR) up to 20 mm/h; (iii) C-reactive protein (CRP) up to 6 mg/l; (iv) morning stiffness lasting up to 15 min and (v) the absence of systemic manifestations (fever, rash, pericarditis, hepatomegaly, splenomegaly or lymph node swelling).

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
	Patients in IL-1 inhibitors (anakinra or canakinumab) switcher group (n=43 including 7 in scope patients), n (%) unless specified: Female: 22 (52) Mean age at onset: 4.5 (SD 3.2) years Mean age at bDMARD start: 9.6 (SD 4.6) years Mean disease duration: 5.1 (SD 3.9) years Pre-treatment: Steroids: 43 (100) Methotrexate: 36 (83) Other cDMARDs: 20 (47) Biologics: 39 (65) Etanercept: 32 (74) Tocilizimab: 9 (21) Concomitant treatment at enrolment: Steroids: 19 (44) Methotrexate: 18 (42) Other cDMARDs: 4 (10) ESR >20 mm/1 h: 16/31 (52) CRP >6 mg/l: 20/34 (59) Mean JADAS-10: 13.0 (SD 9.8)		Paper states that "1 patient on canakinumab treatment who had MAS discontinued due to intolerance"	monthly thereafter) and the number of patients excluded for this reason was not reported. No baseline demographics and clinical characteristics were reported for the canakinumab prior tocilizumab use group. All patients had previously received steroids and it seems likely that most or all or of the in-scope patients had or were receiving methotrexate. Results for in scope patients were only reported graphically and only for the last observation timepoint (not for 0, 3, 6, 12, 18 and 24 months as for other results) with no mean/median length of follow-up reported for this timepoint. No comparisons were made between follow-up and baseline results. **Source of funding** The BIKeR registry is supported by an unrestricted grant from Pfizer, Germany, Abbvie, Germany, Novartis, Germany and Roche, Germany.
Nishimura K, Hara R, Umebayashi H, Takei S, Iwata N, Imagawa T, et al. Efficacy and safety of canakinumab in	**Inclusion criteria** Patients aged ≥2 to <20 years with a confirmed diagnosis	**Intervention details** Canakinumab 4 mg/kg every 4 weeks subcutaneously without	**Critical outcomes** **Reduction and resolution of symptoms (as measured by the**	This study was appraised using the Joanna Briggs Institute 2017 Critical Appraisal Checklist for Case Series. The

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
systemic juvenile idiopathic arthritis: 48-week results from an open-label phase III study in Japanese patients. Modern Rheumatology. 2020:1-9. **Study location** Japan **Study type** Prospective case series **Study aim** To assess the efficacy and safety of canakinumab in Japanese patients with systemic juvenile idiopathic arthritis **Study dates** Not reported	of SJIA as per International League Against Rheumatism criteria at least 3 months prior to enrolment, including active systemic features, arthritis, and CRP >30 mg/L **Exclusion criteria** Major exclusion criteria were concomitant treatment with another biologic agent or disease-modifying drug (washout of 30 days or ≥5 half-lives), history of active MAS within 6 months before enrolment, hypersensitivity to study drug or biologics, and live-virus vaccination within 3 months before enrolment **Sample size** n=15 in scope patients The study included 19 SJIA patients treated with canakinumab (total sample size). Relevant outcomes for the 15 patients with prior tocilizumab use were extracted for inclusion in this review. **Baseline characteristics**	any dose adjustments given following a screening period of 28 days Median duration of exposure to canakinumab was 337 days and ~65% of patients received treatment for ≥48 weeks **Comparator details** None	**juvenile arthritis disease activity score (JADAS) or similar)** • **Achieving ACR paediatric 30 criteria[25], n (%)** At 8 weeks (n=15): 15 (100%) taken from graph • **Achieving ACR paediatric 50 criteria[25], n (%)** At 8 weeks (n=15): 15 (100%) taken from graph • **Achieving ACR paediatric 70 criteria[25], n (%)** At 8 weeks (n=15): 15 (100%) taken from graph Results were not reported separately for patients treated with prior tocilizumab for these outcomes, only for all patients at 2, 4, 8, 28 and 48 weeks for ACR paediatric 30, 50, 70, 90 and 100. However, the 8-week results for achieving ACR paediatric 30, 50 and 70 criteria were extracted as all patients achieved these outcomes and hence these results will also apply to in-scope patients. **Reduction in corticosteroid use**	appraisal was conducted in relation to the patients within this study who received canakinumab 1. YES 2. YES 3. YES 4. UNCLEAR 5. UNCLEAR 6. NO 7. NO 8. YES 9. NO 10. NO **Other comments** This was a prospective case series, with up to 48 weeks follow-up, which included 19 SJIA patients treated with canakinumab, 15 (79%) of which were previously treated with tocilizumab and included in this review. No baseline demographics were reported for the prior tocilizumab use group. All patients were receiving an oral corticosteroid at baseline and 47% of all patients (9/19) were

[25] Adapted ACR paediatric 30/50/70 criteria was defined as improvements of ≥30%/≥50%/≥70% from baseline in ≥3 of the six variables in JIA core set and no intermittent fever (body temperature ≤38°C) in the preceding week, with no more than one of the six variables worsening by >30%. The six JIA components were the number of joints with active arthritis, the number of joints with a limited range of motion, physician's global assessment (PGA), and patients'/parents' global assessment (PPGA) of disease activity on a 100mm visual analog scale (VAS), standardized CRP level (normal range: 0–10 mg/L), and functional ability (using the Disability Index of the Childhood Health Assessment Questionnaire, on a scale of 0–3.

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
	(n=15) Not reported All patients (n=19), median (min - max), unless specified: Age: 9.0 (1-19) years Female, n (%): 13 (68.4) Disease duration: 5.9 (0.4-17.3) years Concomitant use of oral corticosteroid, n (%): 19 (100) Oral prednisolone equivalent dose: 0.2 (0.08-0.94) mg/kg/day Concomitant use of methotrexate, n (%): 9 (47.4) Prior use of tacrolimus, n (%): 4 (21.1) Prior use of tocilizumab, n (%): 15 (78.9) Prior use of etanercept, n (%): 1 (5.3) Standardized CRP: 198.7 (48.8-1311.4) mg/L Physician's Global Assessment of disease activity (VAS): 77.0 (17-99) mm Parent's or patient's assessment of overall well-being (VAS): 85.0 (40-100) mm Fever in the preceding week, n (%): 19 (100) Number of active joints: 4 (2-36)		**Successful oral corticosteroid tapering[26], n (%)** At 28 weeks (n=15): 11 (73.3%) of which 10 (66.7%) were tapered and 1 (6.7%) was corticosteroid-free 1 out of the 4 patients who did not taper discontinued from the study before 8 weeks. Not clear if this was due to adverse event or efficacy **Important outcomes** None reported **Safety** All patients experienced ≥1 AE during the study Type of adverse events was not reported separately for patients treated with prior tocilizumab	on concomitant methotrexate. Previous use of methotrexate was not reported. Use of anakinra not reported. One patient previously treated with tocilizumab was discontinued from the study before 8 weeks either due to adverse event or efficacy. No details of centre(s) involved reported. Not possible to determine whether the case series is single centre or multicentre. **Source of funding** Novartis Pharma

[26] Dose reduced from >0.8 mg/kg/day to ≤0.5 mg/kg/day, or from ≥0.5 mg/kg/day and ≤0.8 mg/kg/day by ≥0.3 mg/kg/day, or from any initial dose to ≤0.2 mg/kg/day, or any reduction from an initial dose of ≤0.2 mg/kg/day, while maintaining ACR paediatric 30 response.

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
	Number of joints with limitation of motion: 3 (0-16) Child Health Assessment Questionnaire functional disability score: 1.3 (0-3.0)			

Abbreviations: ACR – American College of Rheumatology, AE – adverse event, bDMARDs – biologic disease-modifying anti-rheumatic drugs, cDMARDs – conventional disease-modifying anti-rheumatic drugs, CRP – C-reactive protein; DMARDs – disease-modifying anti-rheumatic drugs, ERP – erythrocyte sedimentation rate, IL – interleukin, IQR – interquartile range, JADAS – juvenile arthritis disease activity score, SJIA – systemic-onset juvenile idiopathic arthritis, SD – standard deviation, VAS – visual analogue scale.

Appendix F Quality appraisal checklists

JBI Critical Appraisal Checklist for Case Series

1. Were there clear criteria for inclusion in the case series?
2. Was the condition measured in a standard, reliable way for all participants included in the case series
3. Were valid methods used for the identification of the condition for all participants included in the case series?
4. Did the case series have consecutive inclusion of participants?
5. Did the case series have complete inclusion of participants?
6. Was there clear reporting of the demographics of the participants in the study?
7. Was there clear reporting of clinical information of the participants?
8. Were the outcomes or follow up results of cases clearly reported?
9. Was there clear reporting of the presenting site(s)/clinic(s) demographic information?
10. Was statistical analysis appropriate?

Appendix G GRADE profiles

Table 1: Question: In patients with SJIA refractory to or intolerant of anakinra or tocilizumab, what is the clinical effectiveness and safety of canakinumab compared with current standard treatment?

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Canakinumab	Current standard treatment	Result (95%CI)		
Reduction and resolution of symptoms (as measured by the juvenile arthritis disease activity score (JADAS) or similar)									
Remission[a] off medication, n (%), follow-up time point not reported									
1 single centre retrospective case series Barut et al 2019	Very serious limitations[1]	Very serious indirectness[2]	Not applicable	Not calculable	n=27	None	3 (11.5%)	Critical	Very low
Minimal disease activity on medication (not defined), n (%), follow-up time point not reported									
1 single centre retrospective case series Barut et al 2019	Very serious limitations[1]	Very serious indirectness[2]	Not applicable	Not calculable	n=27	None	23 (85%)	Critical	Very low
Remission (JADAS-10[b] score ≤1) at last documented response (no further details given), %									
1 multicentre prospective case series	Very serious limitations[3]	Serious indirectness[4]	Not applicable	Not calculable	n=7	None	55% of patients	Critical	Very low

Horneff et al 2017									
Remission (American College of Rheumatology (ACR) criteria[c]) at last documented response (no further details given), %									
1 multicentre prospective case series Horneff et al 2017	Very serious limitations[3]	Serious indirectness[4]	Not applicable	Not calculable	n=7	None	43% of patients	Critical	Very low
Achieving ACR paediatric 30 criteria[d] at 8 weeks, n (%)									
1 prospective case series Nishimura et al 2020	Very serious limitations[5]	Very serious indirectness[6]	Not applicable	Not calculable	n=15	None	15 (100%)	Critical	Very low
Achieving ACR paediatric 50 criteria[d] at 8 weeks, n (%)									
1 prospective case series Nishimura et al 2020	Very serious limitations[5]	Very serious indirectness[6]	Not applicable	Not calculable	n=15	None	15 (100%)	Critical	Very low
Achieving ACR paediatric 70 criteria[d] at 8 weeks, n (%)									
1 prospective case series Nishimura et al 2020	Very serious limitations[5]	Very serious indirectness[6]	Not applicable	Not calculable	n=15	None	15 (100%)	Critical	Very low
Reduction in corticosteroid use									
Successful oral corticosteroid tapering[e] at 28 weeks, n (%)									
1 prospective case series Nishimura et al 2020	Very serious limitations[7]	Very serious indirectness[6]	Not applicable	Not calculable	n=15	None	11 (73.3%) of which 10 (66.7%) were tapered and 1 (6.7%) was corticosteroid-free	Critical	Very low

							1 out of the 4 patients who did not taper discontinued from the study before 8 weeks. Not clear if this was due to adverse event or efficacy		
Changes in systemic features of disease (fever, rash, weight change and hepatosplenomegaly)									
No fever at last documented response (no further details given)									
1 multicentre prospective case series Horneff et al 2017	Very serious limitations[3]	Serious indirectness[4]	Not applicable	Not calculable	n=7	None	85% of patients	Critical	Very low
Safety									
Serious adverse effects									
1 single centre retrospective case series Barut et al 2019	Very serious limitations[9]	Very serious indirectness[2]	Not applicable	Not calculable	n=27	None	*"One patient treated with canakinumab had pneumonia"*	Critical	Very low
Discontinuation of medication due to intolerance									
1 multicentre prospective case series Horneff et al 2017	Very serious limitations[3]	Serious indirectness[4]	Not applicable	Not calculable	n=7	None	*"1 patient on canakinumab treatment who had MAS discontinued due to intolerance"*	Critical	Very low
Experience ≥1 adverse event(s) during the study, n (%)									
1 prospective case series Nishimura et al 2020	Very serious limitations[8]	Very serious indirectness[6]	Not applicable	Not calculable	n=15	None	*"All patients experienced ≥1 AE during the study"*	Critical	Very low

Abbreviations: ACR – American College of Rheumatology, AE – adverse event, JADAS – juvenile arthritis disease activity score, MAS – macrophage activation syndrome.									

1. *Very serious risk of bias due to no baseline characteristics reported for in scope patients, no statistical comparisons reported for results of in scope patients and the use of an unvalidated disease activity score to measure outcome*
2. *Very serious indirectness due to non-comparative case series and only a maximum of 67% of the in scope patients can have been previously treated with tocilizumab so not all the patients followed the intervention as exactly stated in the PICO*
3. *Very serious risk of bias due to no baseline characteristics reported for in scope patients and results only reported graphically with no statistical comparisons reported for results of in scope patients*
4. *Serious indirectness due to non-comparative case series*
5. *Very serious risk of bias due to no baseline characteristics reported for in scope patients, limited reporting of results for in scope patients and no details provided of centre(s) involved. Results were only reported graphically with no statistical comparisons reported*
6. *Very serious indirectness due to non-comparative case series and not known if all in scope patients followed the intervention exactly as exactly stated in the PICO as previous use of methotrexate not reported*
7. *Very serious risk of bias due to no baseline characteristics reported for in scope patients, no statistical comparisons reported for results of in scope patients and no details provided of centre(s) involved*
8. *Very serious risk of bias due to no baseline characteristics reported for in scope patients, no reporting of results for in scope patients and no details provided of centre(s) involved*
9. *Very serious risk of bias due to no baseline characteristics reported for in scope patients and inconsistent reporting of results for this outcome*

a. Remission was defined as lack of fever, rash, serositis, splenomegaly, lymphadenopathy and arthritis, as well as normal levels of erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP)
b. JADAS10 is a composite disease activity score (0-40) for JIA including four measures: active joint count (up to 10 joints), physician's global assessment of disease activity, parent/patient evaluation of the child's overall well-being and erythrocyte sedimentation rate (ESR)
c. ACR preliminary criteria for remission/inactive disease includes: (i) the lowest value of the physician's judgement on global disease activity of 0 on a 100-mm visual analogue scale; (ii) erythrocyte sedimentation rate (ESR) up to 20 mm/h; (iii) C-reactive protein (CRP) up to 6 mg/l; (iv) morning stiffness lasting up to 15 min and (v) the absence of systemic manifestations (fever, rash, pericarditis, hepatomegaly, splenomegaly or lymph node swelling
d. Adapted ACR paediatric 30/50/70 criteria was defined as improvements of ≥30%/≥50%/≥70% from baseline in ≥3 of the six variables in JIA core set and no intermittent fever (body temperature ≤38°C) in the preceding week, with no more than one of the six variables worsening by >30%. The six JIA components were the number of joints with active arthritis, the number of joints with a limited range of motion, physician's global assessment (PGA), and patients'/parents' global assessment (PPGA) of disease activity on a 100mm visual analog scale (VAS), standardized CRP level (normal range: 0–10 mg/L), and functional ability (using the Disability Index of the Childhood Health Assessment Questionnaire, on a scale of 0–3
e. Dose reduced from >0.8 mg/kg/day to ≤0.5 mg/kg/day, or from ≥0.5 mg/kg/day and ≤0.8 mg/kg/day by ≥0.3 mg/kg/day, or from any initial dose to ≤0.2 mg/kg/day, or any reduction from an initial dose of ≤0.2 mg/kg/day, while maintaining ACR paediatric 30 response

Glossary

Adverse event	Any undesirable event experienced by a person while they are having a drug or any other treatment or intervention, regardless of whether the event is suspected to be related to or caused by the drug, treatment or intervention.
Baseline	The set of measurements at the beginning of a study (after any initial 'run-in' period with no intervention), with which subsequent results are compared.
Bias	Systematic (as opposed to random) deviation of the results of a study from the 'true' results, which is caused by the way the study is designed or conducted.
Case series	Reports of several patients with a given condition, usually covering the course of the condition and the response to treatment. There is no comparison (control) group of patients.
Confidence interval	A way of expressing how certain we are about the findings from a study, using statistics. It gives a range of results that is likely to include the 'true' value for the population. A wide confidence interval (CI) indicates a lack of certainty about the true effect of the test or treatment - often because a small group of patients has been studied. A narrow CI indicates a more precise estimate (for example, if a large number of patients have been studied). The CI is usually stated as '95% CI', which means that the range of values has a 95 in a 100 chance of including the 'true' value. For example, a study may state that 'based on our sample findings, we are 95% certain that the

	'true' population blood pressure is not higher than 150 and not lower than 110'. In such a case the 95% CI would be 110 to 150.
GRADE (Grading of recommendations assessment, development and evaluation)	A systematic and explicit approach to grading the quality of evidence and the strength of recommendations developed by the GRADE working group.
PICO (population, intervention, comparison and outcome) framework	A structured approach for developing review questions that divides each question into 4 components: the population (the population being studied); the interventions (what is being done); the comparators (other main treatment options); and the outcomes (measures of how effective the interventions have been).
P-value (p)	The p value is a statistical measure that indicates whether or not an effect is statistically significant. For example, if a study comparing 2 treatments found that 1 seems to be more effective than the other, the p value is the probability of obtaining these results by chance. By convention, if the p value is below 0.05 (that is, there is less than a 5% probability that the results occurred by chance), it is considered that there probably is a real difference between treatments. If the p value is 0.001 or less (less than a 0.1% probability that the results occurred by chance), the result is seen as highly significant. If the p value shows that there is likely to be a difference between treatments, the confidence interval describes how big the difference in effect might be.
Retrospective study	A research study that focuses on the past and present. The study examines past exposure to suspected risk factors for the disease or condition. Unlike prospective studies, it does not cover

	events that occur after the study group is selected.
Statistical significance	A statistically significant result is one that is assessed as being due to a true effect rather than random chance.

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