NHS England evidence review:

Canakinumab for patients with Still's disease refractory to anakinra and tocilizumab (adults and children 2 years and over)

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Canakinumab for patients with adult-onset Still's disease (AOSD) 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 adult-onset Still's disease (AOSD) refractory to or intolerant of anakinra and tocilizumab.

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 AOSD consists of non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids. Once the diagnosis is confirmed, a disease-modifying antirheumatic drug (DMARD), such as methotrexate or azathioprine, can be added for patients who fail to achieve remission, or for those who are dependent on steroids for symptomatic control.

For those patients where remission is not achieved following treatment with two DMARDs (or if they are contraindicated) there are two options:

1. For patients with a polyarticular AOSD; tocilizumab can be used (switching to anakinra if further systemic flares occur or there is no response to tocilizumab)
2. For patients with a refractory AOSD; anakinra can be used (switching to tocilizumab if there is no response to treatment with anakinra).

Canakinumab is licensed for the treatment of AOSD and systemic juvenile idiopathic arthritis (SJIA) 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).

2. Executive summary of the review

One paper was included in the evidence review (Colafranesco et al 2017).

This was a multicentre retrospective case series of 140 adults diagnosed with adult-onset Still's disease (AOSD) treated with interleukin-1 (IL-1) inhibitors (anakinra and canakinumab) after failure of therapy based on non-steroidal anti-inflammatory drugs (NSAIDs) and immunosuppressive drugs, and in some cases biologic agents other than IL-1 inhibitors. All patients were treated with anakinra and subsequently four patients were switched to canakinumab after failure of anakinra. Results for these four patients were extracted for inclusion in this evidence review.

Research Question 1:

1. In patients with AOSD 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 disease activity score (DAS28) 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 disease activity score (DAS28) or similar)

One retrospective case series (Colafrancesco et al 2017) (n=4) provided non-comparative evidence on the reduction and resolution of symptoms as measured by

a modified version of the Pouchot's disease activity score[1] from baseline to 12 months in four AOSD patients treated with canakinumab after failed anakinra with or without prior tocilizumab. Mean Pouchot's score improved significantly from baseline to 3 months (4.25 (standard deviation (SD) 2.6; range 2 to 8) vs 1.25 (SD 1.8; range 1 to 4); p<0.0001; n=4), baseline to 6 months (1.5 (SD and range not reported); p<0.0001; n=4), and baseline to 12 months (1.0 (SD and range not reported); p<0.0001; n=3). Pouchot's scores were estimated from a bar chart for 6 and 12 month follow-up results.

Reduction in corticosteroid use

One retrospective case series (Colafrancesco et al 2017) (n=4) provided non-comparative evidence on the reduction in corticosteroid use from baseline to 12 months in four AOSD patients treated with canakinumab after failed anakinra with or without prior tocilizumab. All patients were on concomitant corticosteroids at baseline and no patients discontinued use during the 12 months study period. Mean prednisone dosage significantly reduced from baseline to 3 months (143.7 mg (SD 238.2) vs 8.2 mg (SD 7.8; p<0.0001; n=4) and baseline to 12 months (10 mg (SD 7.1); p<0.0001; n=3). Mean prednisone dosage was lower compared to baseline at 6 months (16.2 mg (SD 13); n=4), but statistical significance was not reported.

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 was very low when assessed using modified GRADE.

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

One retrospective case series (Colafrancesco et al 2017) (n=4) provided non-comparative evidence on the control of CRP and ESR from baseline to 12 months in four AOSD patients treated with canakinumab after failed anakinra with or without

[1] Modified Pouchot's score (range 0 to 12), which assigns 1 point to each of 12 disease-related manifestations (fever, evanescent rash, pleuritis, pneumonia, pericarditis, hepatomegaly, serum ferritin levels (>3000 mg/L), lymphadenopathy, white blood cells count (>15,000/mm), sore throat, myalgias, and arthritis).

prior tocilizumab. The study reported that CRP was elevated at baseline and at 3 months in all four patients and decreased in two patients at 6 months and in another patient at 12 months. ESR was reported to be elevated at baseline and at 3 months in 3 patients and reduced in one patient after 6 months and in another patient after 12 months.

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

One retrospective case series (Colafrancesco et al 2017) (n=4) provided non-comparative evidence on the control of CRP and ESR from baseline to 12 months in four AOSD patients treated with canakinumab after failed anakinra with or without prior tocilizumab. The number of patients with fever reduced from all four patients at baseline to one patient (25%) at 3 months, two patients (50%) at 6 months, and no patients at 12 months. The number of patients with rash reduced from two patients (50%) at baseline to 0 patients at 3, 6 months, and 12 months. The number of patients with hepatomegaly or increased liver enzymes remained at one patient throughout the 12 month study period.

Research Question 2

2. In patients with AOSD 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, 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

One retrospective case series (Colafrancesco et al 2017) (n=4) provided non-comparative evidence on adverse effects for the 12 month study period in four AOSD patients treated with canakinumab after failed anakinra with or without prior tocilizumab. The paper reported that no adverse events were registered in the canakinumab treated patients.

Research Question 3:

3. In patients with AOSD 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

Results should be treated with caution as they are limited to four patients within a single, retrospective case series of 140 patients. Limited baseline demographic and clinical characteristics for these four patients were reported. All patients received concomitant corticosteroids and conventional DMARDs either prior to canakinumab (two patients) or in combination with canakinumab (two patients), and two patients received tocilizumab prior to anakinra. Two out of the four patients treated with canakinumab were strictly not in scope as they received biologic DMARDs other than tocilizumab, anakinra and canakinumab. One patient received infliximab, etanercept, adalimumab and tocilizumab prior to anakinra and the other patient received adalimumab. Results were not reported separately for each patient, only for the canakinumab treated patient sub-group at baseline, 3, 6 and 12 months after commencement of canakinumab. One patient (prior treatment not reported) discontinued canakinumab at 9 months due to loss of efficacy and was excluded from the 12 month follow-up results. The measure used to evaluate disease activity (Pouchot's score) has not been validated and results for this outcome at the 6 and 12 month follow-up were presented in a bar chart only, so scores were estimated against the y axis.

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 (NSAIDs and corticosteroids, DMARDs, and anakinra and/or tocilizumab) compared to standard treatment alone in patients with AOSD refractory to or intolerant of anakinra and tocilizumab. The evidence is limited to four patients within a single, retrospective case series of 140 patients and suggests that, compared to baseline, canakinumab improves disease severity and symptoms, reduces concomitant prednisone corticosteroid dosage and reduces biomarkers of inflammation (CRP and ESR) with no adverse events. 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 AOSD refractory to or intolerant of anakinra or tocilizumab, what is the clinical effectiveness of canakinumab compared with current standard treatment?

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

3. In patients with AOSD 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

One paper was identified for inclusion (Colafrancesco et al 2017). Table 1 provides a summary of this included study and full details are given in Appendix E.

The study was a multicentre, retrospective case series. Results were extracted for patients who were treated with canakinumab following anakinra.

No cost effectiveness studies were identified.

Table 1 Summary of included studies

Study	Population	Intervention and comparison	Outcomes reported
Colafrancesco et al 2017 Retrospective case series Italy	140 adults diagnosed with AOSD and treated with IL-1-inhibitors after failure of therapy based on NSAIDs and immunosuppressive drugs, such as steroids and cDMARDs, and in some cases biologic agents other than IL-1 inhibitors Only data for the 4 patients who received canakinumab following anakinra treatment were extracted for	**Intervention** Canakinumab 150 mg every 8 weeks without dose adjustments Mean duration of therapy: 22.1 (+/- 16.5) months Concomitant treatments: 2 patients received canakinumab in association with other DMARDs. 2 patients received canakinumab monotherapy. Previous treatments: • All 4 patients were previously treated with anakinra • The 2 patients on canakinumab	**Critical outcomes** • Reduction and resolution of symptoms as measured by the modified Pouchot's disease activity score[2] at 3, 6 and 12 months • Concomitant prednisone use at 3, 6 and 12 months • Prednisone dosage at 3, 6 and 12 months **Important outcomes** • Control of C-reactive protein and erythrocyte sedimentation rate at 3, 6 and 12 months • Changes in fever, rash and hepatosplenomegaly or increased liver enzymes at 3, 6 and 12 months

[2] Modified Pouchot's score (range 0 to 12), which assigns 1 point to each of 12 disease-related manifestations (fever, evanescent rash, pleuritis, pneumonia, pericarditis, hepatomegaly, serum ferritin levels (>3000 mg/L), lymphadenopathy, white blood cells count (>15,000/mm), sore throat, myalgias, and arthritis).

	inclusion in this review No subgroups results reported for patients in scope	monotherapy were previously treated with other cDMARDs including methotrexate, hydroxychloroquine and cyclosporine A • Before starting anakinra treatment, 3 patients were unsuccessfully treated with other bDMARDs: ○ 1 patient with infliximab, etanercept, adalimumab, and tocilizumab (out of scope) ○ 1 patient with tocilizumab (in scope) ○ 1 patient with adalimumab (out of scope) **Comparison** None	Safety • Number of registered adverse events at 3, 6 and 12 months
Abbreviations: AOSD – adult onset Still's disease, IL – interleukin, NSAIDs – non-steroidal anti-inflammatory drugs, bDMARDs – biologic disease-modifying anti-rheumatic drugs; cDMARDs – conventional disease-modifying anti-rheumatic drugs, DMARDs – disease-modifying anti-rheumatic drugs.			

5. Results

In patients with AOSD 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 disease activity score (DAS28) or similar) **Certainty of evidence:** Very low	Improvement in symptoms is important to patients because this could help determine treatment choice (such as reduction of corticosteroids) and because of the impact on the patient's function and activities of daily living. Resolution of symptoms also indicates clinical remission. One retrospective case series (Colafrancesco et al 2017) (n=140) provided non-comparative evidence on the reduction and resolution of symptoms as measured by a modified version of the Pouchot's disease activity score[3] at 3, 6 and 12 months in four AOSD patients (mean age 34.2 (+/- 15.4) years; three systemic disease and one chronic articular profile). Patients were treated with canakinumab (two patients on monotherapy and two in combination with cDMARDs) after failure of therapy

[3] Modified Pouchot's score (range 0 to 12), which assigns 1 point to each of 12 disease-related manifestations (fever, evanescent rash, pleuritis, pneumonia, pericarditis, hepatomegaly, serum ferritin levels (>3000 mg/L), lymphadenopathy, white blood cells count (>15,000/mm), sore throat, myalgias, and arthritis).

	based on NSAIDs, immunosuppressive drugs and anakinra with or without prior tocilizumab. Two patients also received other biologic agents (infliximab, etanercept and/or adalimumab) prior to anakinra and therefore are not strictly in scope. One patient (prior treatment not reported) discontinued canakinumab at 9 months due to loss of efficacy and was excluded from the 12 month follow-up results. Mean Pouchot's scores were estimated from a bar chart for 6 and 12 month follow-up results. At 3 months: • 1 case series (Colafrancesco et al 2017) (n=4) provided non-comparative evidence that mean Pouchot's score improved significantly (p<0.0001) from 4.25 (SD 2.6; range 2 to 8) to 1.25 (SD 1.8; range 1 to 4) in patients with AOSD treated with canakinumab after failed anakinra (with or without prior tocilizumab) therapy. **(VERY LOW)** At 6 months: • 1 case series (Colafrancesco et al 2017) (n=4) provided non-comparative evidence that Pouchot's score improved statistically significantly (p<0.0001) from 4.25 (SD 2.6; range 2 to 8) to 1.5 (estimated from bar chart) in patients with AOSD treated with canakinumab after failed anakinra (with or without prior tocilizumab) therapy. **(VERY LOW)** At 12 months: • 1 case series (Colafrancesco et al 2017) (n=3) provided non-comparative evidence that Pouchot's score improved statistically significantly (p<0.0001) from 4.25 (SD 2.6; range 2 to 8) to 1.0 (estimated from bar chart) in patients with AOSD treated with canakinumab after failed anakinra (with or without prior tocilizumab) therapy. **(VERY LOW)** **This study provided very low certainty evidence that compared to baseline, canakinumab improves symptoms as measured by a modified version of the Pouchot's disease**

	activity score up to 12 months in patients with AOSD refractory to or intolerant of anakinra and tocilizumab.
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 retrospective case series (Colafrancesco et al 2017) (n=140) provided non-comparative evidence on concomitant corticosteroid use and mean dosage at 3, 6 and 12 months in four AOSD patients (mean age 34.2 (+/- 15.4) years; three systemic disease and one chronic articular profile). Patients were treated with canakinumab (2 patients on monotherapy and 2 in combination with cDMARDs) after failure of therapy based on NSAIDs, immunosuppressive drugs and anakinra with or without prior tocilizumab. Two patients also received other biologic agents (infliximab, etanercept and/or adalimumab) prior to anakinra and therefore are not strictly in scope. One patient (prior treatment not reported) discontinued canakinumab at 9 months due to loss of efficacy and was excluded from the 12 month follow-up results. At 3 months: • 1 case series (Colafrancesco et al 2017) (n=4) provided non-comparative evidence that concomitant corticosteroid use did not change with no discontinuation of use reported in patients with AOSD treated with canakinumab after failed anakinra (with or without prior tocilizumab) therapy. **(VERY LOW)** • 1 case series (Colafrancesco et al 2017) (n=4) provided non-comparative evidence that mean prednisone dosage (8.2 mg; SD 7.8) was statistically significantly lower ($p<0.0001$) compared to baseline (143.7 mg; SD 238.2). **(VERY LOW)**

	At 6 months: • 1 case series (Colafrancesco et al 2017) (n=4) provided non-comparative evidence that concomitant corticosteroid use did not change with no discontinuation of use in patients with AOSD treated with canakinumab after failed anakinra (with or without prior tocilizumab) therapy. **(VERY LOW)** • 1 case series (Colafrancesco et al 2017) (n=4) provided non-comparative evidence that mean prednisone dosage (16.2 mg; SD 13) was lower compared to baseline (143.7 mg; SD 238.2). Statistical significance not reported. **(VERY LOW)** At 12 months: • 1 case series (Colafrancesco et al 2017) (n=3) provided non-comparative evidence that concomitant corticosteroid use did not change with no discontinuation of use in patients with AOSD treated with canakinumab after failed anakinra (with or without prior tocilizumab) therapy. **(VERY LOW)** • 1 case series (Colafrancesco et al 2017) (n=3) provided non-comparative evidence that mean prednisone dosage (10 mg; SD 7.1) was statistically significantly lower ($p<0.0001$) compared to baseline (143.7 mg; SD 238.2). **(VERY LOW)** **This study provided very low certainty evidence that compared to baseline, canakinumab reduces prednisone corticosteroid dosage up to 12 months in patients with AOSD refractory to or intolerant of anakinra and tocilizumab.**
Important outcomes	

Control of biochemical markers of inflammation (CRP, SAA and ESR) **Certainty of evidence:** Very low	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. One retrospective case series (Colafrancesco et al 2017) (n=140) provided non-comparative evidence on the control of CRP and ESR at 3, 6 and 12 months in four AOSD patients (mean age 34.2 (+/- 15.4) years; three systemic disease and one chronic articular profile). Patients were treated with canakinumab (two patients on monotherapy and two in combination with cDMARDs) after failure of therapy based on NSAIDs, immunosuppressive drugs and anakinra with or without prior tocilizumab. Two patients also received other biologic agents (infliximab, etanercept and/or adalimumab) prior to anakinra and therefore are not strictly in scope. One patient (prior treatment not reported) discontinued canakinumab at 9 months due to loss of efficacy and was excluded from the 12 month follow-up results. Up to 12 months: • 1 case series (Colafrancesco et al 2017) (n=4, up to 9 months; n=3, 9 to 12 months) provided non-comparative evidence that “CRP was higher at baseline and after 3 months in all of the patients, it was decreased in two patients at the 6 months time point, and in another at the 12 months time point” in patients with AOSD treated with canakinumab after failed anakinra (with or without prior tocilizumab) therapy. No further details were reported. **(VERY LOW)** • 1 case series (Colafrancesco et al 2017) (n=4, up to 9 months; n=3, 9 to 12 months) provided non-comparative evidence that **“**ESR was elevated at baseline and at the end of the third month in 3 of the 4 patients; it was reduced in one patient after 6 months, and it was reduced in another after 12 months” in patients with AOSD treated

	with canakinumab after failed anakinra (with or without prior tocilizumab) therapy. No further details were reported. **(VERY LOW)** **This study provided very low certainty evidence that compared to baseline, canakinumab reduces biomarkers of inflammation (CRP and ESR) up to 12 months in patients with AOSD refractory to or intolerant of anakinra and tocilizumab.**
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 retrospective case series (Colafrancesco et al 2017) (n=140) provided non-comparative evidence on the changes in fever, rash and hepatosplenomegaly or increased liver enzymes at 3, 6 and 12 months in four AOSD patients (mean age 34.2 (+/- 15.4) years; three systemic disease and one chronic articular profile). Patients were treated with canakinumab (two patients on monotherapy and two in combination with cDMARDs) after failure of therapy based on NSAIDs, immunosuppressive drugs and anakinra with or without prior tocilizumab. Two patients also received other biologic agents (infliximab, etanercept and/or adalimumab) prior to anakinra and therefore are not strictly in scope. One patient (prior treatment not reported) discontinued canakinumab at 9 months due to loss of efficacy and was excluded from the 12 month follow-up results. At 3 months: • 1 case series (Colafrancesco et al 2017) (n=4) provided non-comparative evidence that the number of patients with fever reduced compared to baseline (4 patients (100%) vs 1 (25%)) in patients with AOSD treated with canakinumab after failed anakinra (with or without prior

	tocilizumab) therapy. Statistical significance not reported. **(VERY LOW)** • 1 case series (Colafrancesco et al 2017) (n=4) provided non-comparative evidence that the number of patients with rash reduced compared to baseline (2 patients (50%) vs 0 (0%)) in patients with AOSD treated with canakinumab after failed anakinra (with or without prior tocilizumab) therapy. Statistical significance not reported. **(VERY LOW)** • 1 case series (Colafrancesco et al 2017) (n=4) provided non-comparative evidence that there was no change in the number of patients with hepatomegaly or increased liver enzymes compared to baseline (1 patient (25%) vs 1 (25%)) in patients with AOSD treated with canakinumab after failed anakinra (with or without prior tocilizumab) therapy. Statistical significance not reported. **(VERY LOW)** At 6 months: • 1 case series (Colafrancesco et al 2017) (n=4) provided non-comparative evidence that the number of patients with fever reduced compared to baseline (4 patients (100%) vs 2 (50%)) in patients with AOSD treated with canakinumab after failed anakinra (with or without prior tocilizumab) therapy. Statistical significance not reported. **(VERY LOW)** • 1 case series (Colafrancesco et al 2017) (n=4) provided non-comparative evidence that the number of patients with rash reduced compared to baseline (2 patients (50%) vs 0 (0%)) in patients with AOSD treated with canakinumab after failed anakinra (with or without prior tocilizumab) therapy. Statistical significance not reported. **(VERY LOW)**

	• 1 case series (Colafrancesco et al 2017) (n=4) provided non-comparative evidence that there was no change in the number of patients with hepatomegaly or increased liver enzymes compared to baseline (1 patient (25%) vs 1 (25%)) in patients with AOSD treated with canakinumab after failed anakinra (with or without prior tocilizumab) therapy. Statistical significance not reported. **(VERY LOW)** At 12 months: • 1 case series (Colafrancesco et al 2017) (n=3) provided non-comparative evidence that the number of patients with fever reduced compared to baseline (4 patients (100%) vs 0 (0%)) in patients with AOSD treated with canakinumab after failed anakinra (with or without prior tocilizumab) therapy. Statistical significance not reported. **(VERY LOW)** • 1 case series (Colafrancesco et al 2017) (n=3) provided non-comparative evidence that the number of patients with rash reduced compared to baseline (2 patients (50%) vs 0 (0%)) in patients with AOSD treated with canakinumab after failed anakinra (with or without prior tocilizumab) therapy. Statistical significance not reported. **(VERY LOW)** • 1 case series (Colafrancesco et al 2017) (n=3) provided non-comparative evidence that there was no change in the number of patients with hepatomegaly or increased liver enzymes compared to baseline (1 patient (25%) vs 1 (33%)) in patients with AOSD treated with canakinumab after failed anakinra (with or without prior tocilizumab) therapy. Statistical significance not reported. **(VERY LOW)** **This study provided very low certainty evidence that compared to baseline, canakinumab reduces fever and rash**

	and has no effect on hepatosplenomegaly up to 12 months in patients with AOSD refractory to or intolerant of anakinra and 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. One retrospective case series (Colafrancesco et al 2017) (n=140) provided non-comparative evidence on the number of registered adverse events at 3, 6 and 12 months in four AOSD patients (mean age 34.2 (+/- 15.4) years; three systemic disease and one chronic articular profile). Patients were treated with canakinumab (two patients on monotherapy and two in combination with cDMARDs) after failure of therapy based on NSAIDs, immunosuppressive drugs and anakinra with or without prior tocilizumab. Two patients also received other biologic agents (infliximab, etanercept and/or adalimumab) prior to anakinra and therefore are not strictly in scope. One patient (prior treatment not reported) discontinued canakinumab at 9 months due to loss of efficacy and was excluded from the 12 month follow-up results. Up to 12 months: • 1 case series (Colafrancesco et al 2017) (n=4, up to 9 months; n=3, 9 to 12 months) provided non-comparative evidence that there were no adverse events registered in patients with AOSD treated with canakinumab after failed anakinra (with or without prior tocilizumab) therapy. **(VERY LOW)** **This study provided very low certainty evidence on the safety of canakinumab up to 12 months in patients with AOSD refractory to or intolerant of anakinra and tocilizumab.**

Abbreviations: AOSD – adult onset Still's disease, cDMARDs – conventional disease-modifying anti-rheumatic drugs, CRP – C-reactive protein, DMARDs – disease-modifying anti-rheumatic drugs, ESR – erythrocyte sedimentation rate, NSAIDs – non-steroidal anti-inflammatory drugs, SAA – serum amyloid A, SD – standard deviation.

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 as 4th line treatment.

In patients with AOSD 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 (NSAIDs and corticosteroids, DMARDs, and anakinra and/or tocilizumab) compared with standard treatment alone in patients with AOSD refractory to or intolerant of anakinra and tocilizumab. The critical outcomes of interest were improvement in quality of life, reduction and resolution of symptoms (as measured by the disease activity score (DAS28) 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 AOSD patients needed to be treated with canakinumab as fourth line treatment following first line treatment with NSAIDs and corticosteroids, second line treatment with immunosuppressive therapies (including methotrexate, ciclosporin, azathioprine, leflunomide or mycophenolate or where standard therapies are contraindicated), and third line treatment with tocilizumab and/or anakinra. Very limited evidence was available with only results of four patients extracted from a case series (Colafrancesco et al 2017) designed to assess the effectiveness of anakinra and canakinumab in patients with AOSD found to be refractory to other therapies.

Colafrancesco et al 2017 was a multicentre (18 centres) retrospective case series of 140 patients with AOSD treated with IL-1-inhibitors (anakinra and canakinumab) after failure of therapy based on NSAIDs and immunosuppressive drugs, and in some cases other biologic agents. All 140 patients received anakinra, four of which were switched to canakinumab after failed anakinra. Relevant outcomes for these four patients were extracted for inclusion in this review.

Results from the four canakinumab treated patients provided limited evidence for reduction and resolution of symptoms as measured by the disease activity score and reduction in corticosteroid use (critical outcomes), control of CRP and ESR and changes in fever, rash and hepatosplenomegaly (important outcomes), and safety outcomes. No evidence was available for the other outcomes of interest. The case

series was at very high risk of bias due to its retrospective, non-comparative study design and the requirement of data extraction for four patients in scope out of the 140 patients included in the study. Certainty in the evidence for critical and important outcomes was very low when assessed using modified GRADE.

Results for the sub-group of four patients should be treated with caution. Limited baseline demographic and clinical characteristics for these patients were reported. All patients received concomitant corticosteroids and conventional DMARDs either prior to canakinumab (two patients) or in combination with canakinumab (two patients), and two patients received tocilizumab prior to anakinra. Two out of the four patients treated with canakinumab did not directly follow the intervention as stated in the PICO as they received biologic DMARDs other than tocilizumab, anakinra and canakinumab. One patient received infliximab, etanercept, adalimumab and tocilizumab prior to anakinra and the other patient received adalimumab. Results were not reported separately for each patient, only for the canakinumab treated patient sub-group at baseline, 3, 6 and 12 months after commencement of canakinumab. One patient (prior treatment not reported) discontinued canakinumab at 9 months due to loss of efficacy and was excluded from the 12 month follow-up results. The measure used to evaluate disease activity (Pouchot's score) has not been validated and results for this outcome at the 6 and 12 month follow-up were presented in a bar chart only, so scores were estimated against the y axis.

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 (NSAIDs and corticosteroids, DMARDs, and anakinra and/or tocilizumab) compared to standard treatment alone in patients with AOSD refractory to or intolerant of anakinra or 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 a small sub-group within a case series.

Very limited evidence was identified with results for only four patients treated with canakinumab extracted from a retrospective case series with up to 12 months follow-up designed to assess the effectiveness of anakinra and canakinumab in 140 patients with AOSD found to be refractory to other therapies. All four patients were previously treated with anakinra, half of which also received tocilizumab. The results from this subgroup of four patients should be treated with caution due to the small sample size and half of the patients being previously treated with biologic DMARDs not in scope (infliximab, etanercept and/or adalimumab). Furthermore, one patient (previous treatments not reported) discontinued canakinumab at 9 months due to loss of efficacy and was excluded from the 12 month follow-up results.

This very low certainty, non-comparative evidence for four patients with AOSD refractory to or intolerant of anakinra and tocilizumab suggests that canakinumab, compared to baseline, improves disease severity and symptoms, reduces concomitant prednisone corticosteroid dosage and reduces biomarkers of inflammation (CRP and ESR) with no adverse events.

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 AOSD refractory to or intolerant of anakinra or tocilizumab, what is the clinical effectiveness of canakinumab compared with current standard treatment?

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

3. In patients with AOSD 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 adult-onset Still's disease (AOSD) that are refractory or intolerant to anakinra or tocilizumab. *Adult-onset Still's disease (AOSD) is a rare, multisystem autoinflammatory disorder that can cause symptoms of fever, polyarthritis, lymphadenopathy, evanescent rash and sore throat amongst other clinical manifestations.*
I – Intervention	Canakinumab as 4th line treatment, after: 1. Non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids 2. Immunosuppressive therapies (including methotrexate, ciclosporin, azathioprine, leflunomide or mycophenolate or where standard therapies are contraindicated[4]) 3. Anakinra or tocilizumab followed by the other

[4] In England, two immunosuppressive therapies must be used before 3rd line treatment

	Canakinumab is a recombinant human monoclonal antibody that is proposed as a 4th line treatment option for patients with AOSD 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: 1. Non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids 2. Immunosuppressive therapies (including methotrexate, ciclosporin, azathioprine, leflunomide or mycophenolate or where standard therapies are contraindicated) 3. Tocilizumab or anakinra followed by the other *Current standard treatment for AOSD involves three lines of treatment. First line treatment is with non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids, followed if necessary by treatment with a disease-modifying antirheumatic drug (DMARD). If remission is not achieved following treatment with two DMARDs, third line treatment is with tocilizumab and/or anakinra depending on the type of AOSD and treatment response.*
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 AOSD.* **Clinical Effectiveness** *Critical to decision-making:* • Quality of life: preferred measure is the Health Assessment Questionnaire (HAQ) or similar. *This questionnaire assesses quality of life 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 disease activity score (DAS28) or similar). *Improvement in symptoms is important to patients because this could help determine treatment choice (such as reduction of corticosteroids) and because of the 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

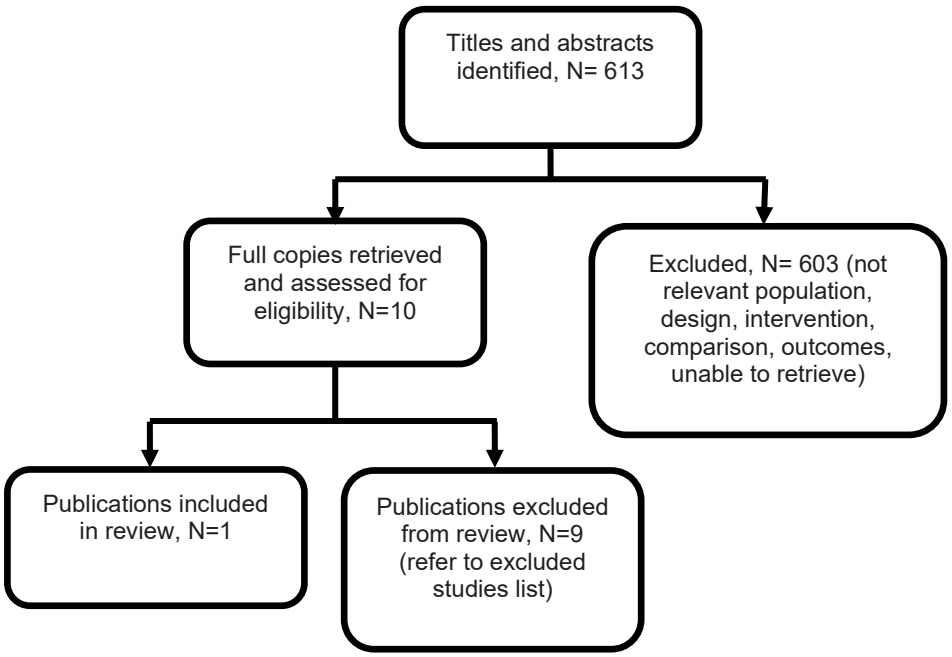
Medline search

# ▲	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 10 references were obtained in full text and assessed for relevance. Of these, 1 reference is included in the evidence summary. The remaining 9 references were excluded and are listed in Appendix D.

Figure 1- Study selection flow diagram



References submitted with Preliminary Policy Proposal

Reference	Paper Selection decision and rationale if excluded
Sfriso, P., Bindoli, S., Doria, A., Feist, E., Galozzi, P. (2020) Canakinumab for the treatment of adult-onset Still's disease. Expert Review of Clinical Immunology. 18:1-10.	Excluded. Narrative review.
Cavalli, G., Tomelleri, A., De Luca, G., Campochiaro, C., Dinarello, C.A., Baldissera, E., Dagna, L. (2019) Efficacy of canakinumab as first-line biologic agent in adult-onset Still's disease. Arthritis Research and Therapy. 21(1):54.	Excluded. Intervention is out of scope as canakinumab is third line treatment after corticosteroids and methotrexate (i.e. canakinumab not fourth line treatment following anakinra or tocilizumab). Letter.

Appendix D Excluded studies table

Study reference	Reason for exclusion
Cavalli G, Tomelleri A, De Luca G, Campochiaro C, Dinarello CA, Baldissera E, et al. Efficacy of canakinumab as first-line biologic agent in adult-onset Still's disease. Arthritis Res Ther. 2019;21(1):54.	Excluded on the grounds that the intervention is out of scope i.e. 3rd line canakinumab (no anakinra or tocilizumab) plus published as a letter which is also out of scope
Colafrancesco S, Manara M, Bortoluzzi A, Serban T, Bianchi G, Cantarini L, et al. Management of adult-onset Still's disease with interleukin-1 inhibitors: evidence- and consensus-based statements by a panel of Italian experts. Arthritis Research & Therapy. 2019;21(1):275.	Not specific to canakinumab or 4th line treatment. Includes results of 3 studies of canakinumab patients but does not give previous treatments for these patients: Maria et al 2014 (case report), Colafrancesco et al 2017 (included in RER) and Rossi-Semerano et al 2015 (excluded from RER)
Garcia FJN, Pascual M, Lopez De Recalde M, Juarez P, Morales-Ivorra I, Notario J, et al. Adult-onset Still's disease with atypical cutaneous manifestations. Medicine (United States). 2017;96(11).	Only case 1 is in scope (case report) and no results are reported specifically for this patient. Case reports are usually filtered out at an earlier stage of paper selection. It is inconsistent with the exclusion criteria to include this case report, only because it was included in a report of more than one patient
Kedor C, Listing J, Zernicke J, Weis A, Behrens F, Blank N, et al. Canakinumab for Treatment of Adult-Onset Still's Disease to Achieve Reduction of Arthritic Manifestation (CONSIDER): phase II, randomised, double-blind, placebo-controlled, multicentre, investigator-initiated trial. Annals of the Rheumatic Diseases. 2020;79(8):1090-7.	Population is not AOSD patients who are refractory or intolerant to anakinra or tocilizumab. Population inclusion criteria are AOSD with active joint disease. Previous treatments are not considered. Baseline characteristics show that 72 to 77% of patients were on previous bDMARDS, 67 to 77% were on previous anakinra, 12 to 22% on previous tocilizumab. No results specific to patients who failed or could not tolerate 3rd line treatment
Kontzias A, Efthimiou P. The use of Canakinumab, a novel IL-1beta long-acting inhibitor, in refractory adult-onset Still's disease. Seminars in Arthritis & Rheumatism. 2012;42(2):201-5.	Only Case 1 is in scope (case report). Case reports are usually filtered out at an earlier stage of paper selection. It is inconsistent with the exclusion criteria to include this case report, only because it was included in a report of more than one patient. Case 2 is out of scope as they did not have standard immunosuppressant treatment before anakinra

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.	Does not report results for in scope AOSD patients. Includes 2 AOSD patients on canakinumab, but results not reported separately for this group and not clear if 4th line canakinumab treatment
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 separate results reported for AOSD patients on canakinumab
Youngstein T, Hoffmann P, Gul A, Lane T, Williams R, Rowczenio DM, et al. International multi-centre study of pregnancy outcomes with interleukin-1 inhibitors. Rheumatology. 2017;56(12):2102-8.	Case series does not include any AOSD patients on canakinumab
Zhou S, Qiao J, Bai J, Wu Y, Fang H. Biological therapy of traditional therapy-resistant adult-onset Still's disease: an evidence-based review. Ther Clin Risk Manag. 2018;14:167-71.	Not specific to canakinumab or canakinumab 4th line treatment. No results for canakinumab as 4th line treatment

Appendix E Evidence Table

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
Colafrancesco S, Priori R, Valesini G, Argolini L, Baldissera E, Bartoloni E, et al. Response to Interleukin-1 Inhibitors in 140 Italian Patients with Adult-Onset Still's Disease: A Multicentre Retrospective Observational Study. Frontiers in Pharmacology. 2017;8:369. **Study location** Italy (multicentre; 18 University Hospital centres) **Study type** Retrospective case series	**Inclusion criteria** Adults with AOSD diagnosed in accordance with Yamaguchi's criteria[5] treated with IL-1-inhibitors after failure of therapy based on NSAIDs and immunosuppressive drugs, such as steroids and DMARDs, and in some cases other biologic agents. **Exclusion criteria** Not stated **Sample size** n=4 The study includes 140 AOSD patients all of which were treated with anakinra. Relevant outcomes for the 4 patients who were later switched to canakinumab after anakinra failed were extracted for inclusion in this review. **Baseline characteristics**	**Intervention details** n=4 Canakinumab: 150 mg every 8 weeks without dose adjustment **Comparator details** None	**Critical outcomes** **Reduction and resolution of symptoms (as measured by the disease activity score (DAS28) or similar)** **Modified Pouchot's score[6], mean (SD)** At baseline (n=4): 4.25 (2.6), range 2 to 8 At 3 months (n=4): 1.25 (1.8), range 1 to 4 Statistically significant reduction from baseline (p<0.0001) At 6 months (n=4): (estimated from bar chart) 1.5 (SD not reported) Statistically significant reduction from baseline (p<0.0001) At 12 months (n=3):	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. No 4. Yes 5. Unclear 6. No 7. Yes 8. Yes 9. No 10. Yes **Other comments** This was a retrospective case series which identified 140 patients with AOSD treated with IL-1-inhibitors after failure of therapy based on NSAIDs and

[5] Diagnosis requires ≥5 criteria including at least 2 or more major criteria. Infections, malignancies, and other rheumatic diseases must be excluded. Major criteria = fever ≥39°C (≥1 week), arthralgia (≥2 weeks), typical rash, leukocytosis (≥10 000/mm^3) with ≥80% of granulocytes. Minor criteria = sore throat, lymphadenopathy and/or splenomegaly, liver dysfunction, negative rheumatoid factor and antinuclear antibody.
[6] Modified Pouchot's score (range 0 to 12), which assigns 1 point to each of 12 disease-related manifestations (fever, evanescent rash, pleuritis, pneumonia, pericarditis, hepatomegaly, serum ferritin levels (>3000 mg/L), lymphadenopathy, white blood cells count (>15,000/mm), sore throat, myalgias, and arthritis).

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
Study aim To evaluate the efficacy and safety of IL-1 inhibitors (anakinra and canakinumab) in a large group of AOSD patients found to be refractory to other therapies **Study dates** Not reported	(n=4) Mean (SD) age at disease onset: 34.2 (15.4) years Mean (SD) age at diagnosis: 34.7 (13.3) years Mean (SD) duration of disease before starting canakinumab: 58.33 (48.4) months Patients presenting with a systemic disease pattern, n (%): 3 (75) Patients presenting with a chronic articular profile: 1 (25) Previous or concomitant therapies, n (%) Current steroids: 4 (100) Previous or current cDMARDs therapy: 4 (100) Previous anakinra therapy: 4 (100) Previous bDMARD therapy before starting anakinra: 3 (75) • 1 patient with infliximab, etanercept, adalimumab and tocilizumab • 1 patient with tocilizumab • 1 patient with adalimumab Current canakinumab in combination with cDMARDs: 2 (50)		estimated from bar chart 1.0 (SD not reported) Statistically significant reduction from baseline (p<0.0001) **Reduction in corticosteroid use** **Concomitant steroid use** At baseline (n=4): 4 (100) At 3 months (n=4): 4 (100) At 6 months (n=4): 4 (100) At 12 months (n=3): 3 (100) **Prednisone dosage, mean (SD)** At baseline (n=4): 143.7 mg (238.2) At 3 months (n=4): 8.2 mg (7.8) Statistically significant change from baseline (p<0.0001) At 6 months (n=4): 16.2 mg (13) Statistical significance of change from baseline not reported At 12 months (n=3) 10 mg (7.1) Statistically significant change from baseline (p<0.0001) **Important outcomes** **Control of biochemical markers of inflammation (C-reactive protein, serum amyloid A and erythrocyte sedimentation rate)** **C-reactive protein**	immunosuppressive drugs, and in some cases other biologic agents. Limited baseline demographics were reported. All patients were treated with anakinra and 4 patients were switched to canakinumab after anakinra failed. Two of these patients met the criteria for inclusion for this review having had 4th line canakinumab treatment after (1) steroids and NSAIDs, (2) cDMARDS, and (3) anakinra or tocilizumab followed by the other. The other 2 patients treated with canakinumab were out of scope as they received other bDMARDs (infliximab, etanercept and adalimumab) prior to anakinra therapy. Results are not reported separately for the 2 patients in scope, only the 4 patients treated with canakinumab. It should also be noted that one patient was discontinued from canakinumab treatment after 9 months due to loss of efficacy and was not included in the 12 month follow-up results. It is not possible to determine whether this patient is in scope. The measure used to evaluate patients' disease activity

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
	Current canakinumab monotherapy: 2 (50)		*"CRP was higher at baseline and after 3 months in all of the patients, it was decreased in two patients at the 6 month time point, and in another at the 12 month time point."* **Erythrocyte sedimentation rate** *"ESR was elevated at baseline and at the end of the third month in 3 of the 4 patients; it was reduced in one patient after 6 months, and it was reduced in another after 12 months."* **Changes in systemic features of disease (fever, rash, weight change and hepatosplenomegaly)** **Fever, n (%)** At baseline (n=4): 4 (100) At 3 months (n=4): 1 (25) At 6 months (n=4): 2 (50) At 12 months (n=3): 0 (0) **Rash, n (%)** At baseline (n=4): 2 (50) At 3 months (n=4): 0 (0) At 6 months (n=4): 0 (0) At 12 months (n=3): 0 (0) **Hepatomegaly or increased liver enzymes, n (%)** At baseline (n=4): 1 (25) At 3 months (n=4): 1 (25) At 6 months (n=4): 1 (25) At 12 months (n=3): 1 (33.3)	(Pouchot's score) has not been validated. Results for biochemical markers of inflammation were described in a narrative format only for patients treated with canakinumab. **Source of funding** Not reported

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
			Safety No adverse events were registered.	

Abbreviations: AOSD – adult onset Still's disease, bDMARDs – biologic disease-modifying anti-rheumatic drugs, cDMARDS – conventional disease-modifying anti-rheumatic drugs, DMARDs – disease-modifying anti-rheumatic drugs, IL – interleukin, NSAIDs – non-steroidal anti-inflammatory drugs, SD – standard deviation.

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

Question: In patients with AOSD 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 disease activity score (DAS28) or similar)									
Modified Pouchot's score[a] at 3 months (benefit is indicated by lower result)									
1 multicentre retrospective case series Colofrancesco et al 2017	Serious limitations[1]	Very serious indirectness[2]	Not applicable	Not calculable	n=4	None	Mean score (SD) Baseline (n=4): 4.25 (2.6), range 2 to 8 3 months (n=4): 1.25 (1.8), range 1 to 4 Statistically significant reduction from baseline (p<0.0001)	Critical	Very low
Modified Pouchot's score at 6 months (estimated from bar chart; benefit is indicated by lower result)									
1 multicentre retrospective case series Colofrancesco et al 2017	Serious limitations[1]	Very serious indirectness[2]	Not applicable	Not calculable	n=4	None	Mean score (SD) Baseline (n=4): 4.25 (2.6), range 2 to 8 6 months (n=4): 1.5 (SD not reported) Statistically significant reduction from baseline (p<0.0001)	Critical	Very low
Modified Pouchot's score at 12 months (estimated from bar chart; benefit is indicated by lower result)									
1 multicentre retrospective case series	Serious limitations[1]	Very serious indirectness[2]	Not applicable	Not calculable	n=3	None	Mean score (SD) Baseline (n=4): 4.25 (2.6), range 2 to 8	Critical	Very low

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)		
Colofrancesco et al 2017							12 months (n=3): estimated from bar chart 1.0 (SD not reported) Statistically significant reduction from baseline (p<0.0001)		
Reduction in corticosteroid use									
Concomitant steroid use at 3 months									
1 multicentre retrospective case series Colofrancesco et al 2017	No serious limitations	Very serious indirectness[2]	Not applicable	Not calculable	n=4	None	Baseline (n=4): 4 (100) 3 months (n=4): 4 (100)	Critical	Very low
Concomitant steroid use at 6 months									
1 multicentre retrospective case series Colofrancesco et al 2017	No serious limitations	Very serious indirectness[2]	Not applicable	Not calculable	n=4	None	Baseline (n=4): 4 (100) 6 months (n=4): 4 (100)	Critical	Very low
Concomitant steroid use at 12 months									
1 multicentre retrospective case series Colofrancesco et al 2017	No serious limitations	Very serious indirectness[2]	Not applicable	Not calculable	n=3	None	Baseline (n=4): 4 (100) 12 months (n=3): 3 (100)	Critical	Very low

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)		
Prednisone dosage at 3 months									
1 multicentre retrospective case series Colofrancesco et al 2017	No serious limitations	Very serious indirectness[2]	Not applicable	Not calculable	n=4	None	Mean (SD) dosage: Baseline (n=4): 143.7 mg (238.2) 3 months (n=4): 8.2 mg (7.8) Statistically significant change from baseline (p<0.0001)	Critical	Very low
Prednisone dosage at 6 months									
1 multicentre retrospective case series Colofrancesco et al 2017	No serious limitations	Very serious indirectness[2]	Not applicable	Not calculable	n=4	None	Mean (SD) dosage: Baseline (n=4): 143.7 mg (238.2) 6 months (n=4): 16.2 mg (13) Statistical significance of change from baseline not reported	Critical	Very low
Prednisone dosage at 12 months									
1 multicentre retrospective case series Colofrancesco et al 2017	No serious limitations	Very serious indirectness[2]	Not applicable	Not calculable	n=3	None	Mean (SD) dosage: Baseline (n=4): 143.7 mg (238.2) 12 months (n=3) 10 mg (7.1) Statistically significant change from baseline (p<0.0001)	Critical	Very low
Control of biochemical markers of inflammation (C-reactive protein, serum amyloid A and erythrocyte sedimentation rate)									
Control of C-reactive protein up to 12 months									
1 multicentre retrospective case series Colofrancesco et al 2017	Serious limitations[3]	Very serious indirectness[2]	Not applicable	Not calculable	n=4 (BL to 6 months)	None	*"CRP was higher at baseline and after 3 months in all of the patients, it was decreased in two patients at the 6 months time point, and in another at the 12 months time point."*	Important	Very low

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)		
					n=3 (12 months)				
Erythrocyte sedimentation rate up to 12 months									
1 multicentre retrospective case series Colofrancesco et al 2017	Serious limitations[3]	Very serious indirectness[2]	Not applicable	Not calculable	n=4 (BL to 6 months) n=3 (12 months	None	*"ESR was elevated at baseline and at the end of the third month in 3 of the 4 patients; it was reduced in one patient after 6 months, and it was reduced in another after 12 months."*	Important	Very low
Changes in systemic features of disease (fever, rash, weight change and hepatosplenomegaly)									
Fever at 3 months									
1 multicentre retrospective case series Colofrancesco et al 2017	No serious limitations	Very serious indirectness[2]	Not applicable	Not calculable	n=4	None	n (%) Baseline (n=4): 4 (100) 3 months (n=4): 1 (25)	Important	Very low
Fever at 6 months									
1 multicentre retrospective case series Colofrancesco et al 2017	No serious limitations	Very serious indirectness[2]	Not applicable	Not calculable	n=4	None	n (%) Baseline (n=4): 4 (100) 6 months (n=4): 2 (50)	Important	Very low

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)		
Fever at 12 months									
1 multicentre retrospective case series Colofrancesco et al 2017	No serious limitations	Very serious indirectness[2]	Not applicable	Not calculable	n=3	None	n (%) Baseline (n=4): 4 (100) 12 months (n=3): 0 (0)	Important	Very low
Rash at 3 months									
1 multicentre retrospective case series Colofrancesco et al 2017	No serious limitations	Very serious indirectness[2]	Not applicable	Not calculable	n=4	None	n (%) Baseline (n=4): 2 (50) 3 months (n=4): 0 (0)	Important	Very low
Rash at 6 months									
1 multicentre retrospective case series Colofrancesco et al 2017	No serious limitations	Very serious indirectness[2]	Not applicable	Not calculable	n=4	None	n (%) Baseline (n=4): 2 (50) 6 months (n=4): 0 (0)	Important	Very low
Rash at 12 months									
1 multicentre retrospective case series Colofrancesco et al 2017	No serious limitations	Very serious indirectness[2]	Not applicable	Not calculable	n=3	None	n (%) Baseline (n=4): 2 (50) 12 months (n=3): 0 (0)	Important	Very low
Hepatomegaly or increased liver enzymes at 3 months									

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)		
1 multicentre retrospective case series Colofrancesco et al 2017	No serious limitations	Very serious indirectness[2]	Not applicable	Not calculable	n=4	None	n (%) Baseline (n=4): 1 (25) 3 months (n=4): 1 (25)	Important	Very low
Hepatomegaly or increased liver enzymes at 6 months									
1 multicentre retrospective case series Colofrancesco et al 2017	No serious limitations	Very serious indirectness[2]	Not applicable	Not calculable	n=4	None	n (%) Baseline (n=4): 1 (25) 6 months (n=4): 1 (25)	Important	Very low
Hepatomegaly or increased liver enzymes at 12 months									
1 multicentre retrospective case series Colofrancesco et al 2017	No serious limitations	Very serious indirectness[2]	Not applicable	Not calculable	n=3	None	n (%) Baseline (n=4): 1 (25) 12 months (n=3): 1 (33.3)	Important	Very low
Adverse effects									
Registered adverse events up to 12 months									
1 multicentre retrospective case series Colofrancesco et al 2017	No serious limitation	Very serious indirectness[2]	Not applicable	Not calculable	n=4 (BL to 6 months) n=3 (12	None	*"No adverse events were registered"*	Important	Very low

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)		
					months				
Abbreviations: BL – baseline, CRP – C-reactive protein, ESR – erythrocyte sedimentation rate, SD – standard deviation.									

1. *Serious risk of bias due to use of unvalidated outcome measure*
2. *Very serious indirectness due to no comparison across treatment arms and 2 out of the 4 patients in scope did not follow the intervention exactly as stated in the PICO*
3. *Serious risk of bias due to unclear reporting of outcome*

a. Modified Pouchot's score (range 0 to 12), which assigns 1 point to each of 12 disease-related manifestations (fever, evanescent rash, pleuritis, pneumonia, pericarditis, hepatomegaly, serum ferritin levels (>3000 mg/L), lymphadenopathy, white blood cells count (>15,000/mm), sore throat, myalgias, and arthritis).

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.
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.
Standard deviation (SD)	A measure of the spread, scatter or variability of a set of measurements. Usually used with the mean (average) to describe numerical data.
Statistical significance	A statistically significant result is one that is assessed as being due to a true effect rather than random chance.

References

Included studies

- Colafrancesco S, Priori R, Valesini G, Argolini L, Baldissera E, Bartoloni E, et al. Response to Interleukin-1 Inhibitors in 140 Italian Patients with Adult-Onset Still's Disease: A Multicentre Retrospective Observational Study. Frontiers in Pharmacology. 2017;8:369.

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