NHS England

Evidence review: Anakinra/Tocilizumab for the treatment Adult Onset Still's Disease refractory to second-line therapy (adults)

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Evidence review: Anakinra / Tocilizumab for the treatment of Adult Onset Still's disease refractory to methotrexate and corticosteroids.

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Contents

1. Introduction

- Adult-onset Still's disease (AOSD) is a relatively rare multisystem autoinflammatory disorder of unknown aetiology with an incidence of approximately 1-2 per million. It is estimated there are between 55-110 incident cases per year and an estimated prevalence of between 400-800 patients in England. Typically patients present with high spiking fever, polyarthritis, lymphadenopathy, evanescent rash, sore throat and a prominent leucocytosis.
- There are a number of other recognised clinical manifestations of AOSD including hepatosplenomegaly, weight loss, myalgia and pericarditis. Diagnosis is difficult due to the wide range of differential diagnoses and lack of specific diagnostic tests. This means that the full spectrum of AOSD may not be recognised.
- Various diagnostic criteria have been developed, but the Yamaguchi classification (Yamaguchi M. et.al. 1992) criteria are most frequently used. Five or more criteria are required of which two or more must be major :

  - Major criteria
  - Fever >39 °C, lasting 1 week or longer
  - Arthralgia or arthritis, lasting 2 weeks or longer
  - Typical rash
  - Leucocytosis >10,000/mm^3 with >80% polymorphonuclear cells

  - Minor criteria
  - Sore throat
  - Recent development of significant lymphadenopathy
  - Hepatomegaly or splenomegaly
  - Abnormal liver function tests
  - Negative tests for antinuclear antibody (IF) and rheumatoid factor (IgM)

  - Exclusion criteria
  - Infections
  - Malignancies (mainly malignant lymphoma)
  - Other rheumatic disease (mainly systemic vasculitides).

- Based on the predominant symptoms, disease activity and evolution, two phenotypes of AOSD have been described. One is a systemic form which has an acute onset. These patients tend to be highly symptomatic with fevers, weight loss and other systemic manifestations (Group 1). In patients with the systemic predominant form, the course of the disease might be monocyclic and self-limiting, intermittent or polycyclic. The current literature suggests that on average 30% of patients develop a monocyclic course, 30% a polycyclic course, and 40% a chronic course.
- The other disease type is the arthritis predominant form of AOSD. This usually has an indolent onset (Group 2). Systemic symptoms are less well defined and a subset of patients develop a chronic erosive arthritis.
- First line treatment for AOSD consists of non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids. NSAIDs can be used for symptomatic control during diagnostic work up. Once the diagnosis is confirmed, patients are initially treated with corticosteroids (0.8-1.0 mg/kg/day). Methotrexate (MTX) (7.5-20 mg/week) can be added for patients who fail to achieve remission or are dependent on steroids for symptomatic control.
- Clinical outcomes following treatment of AOSD include resolution of disease flare, clinical remission, normalisation of biochemical markers (e.g. C-reactive protein (CRP)), improved serum amyloid levels and improvement in quality of life.
- In patients that fail to achieve remission after use of corticosteroids and methotrexate,

the use of anakinra has been suggested as a follow on therapy. Anakinra is a biologic agent that blocks receptors for interleukin-1 (IL-1). IL-1 causes inflammation of joints and joint damage. [Kineret (Anakinra), EMA, 2016].

- Anakinra is licensed by the European Medicines Agency (EMA) for use in rheumatoid arthritis (RA) and cryopyrin-associated periodic syndromes (CAPS). Anakinra is not licensed for use in AOSD.
- NICE has reviewed anakinra for use in rheumatoid arthritis (RA) and does not recommend anakinra for the treatment of RA except in the context of a controlled, long-term clinical study (NICE, 2009). NICE (National Institute for Health and Care Excellence) has not reviewed anakinra for use in AOSD.
- Tocilizumab has also been suggested as a treatment in AOSD patients with the chronic arthritis predominant form (Group 2) refractory to MTX and patients in Group 1 who have failed to respond to MTX and anakinra. Tocilizumab is a monoclonal antibody that attaches to the receptor for interleukin-6 (IL-6) which is responsible for causing inflammation (Tocilizumab – RoActemra, EMA, 2009).
- Tocilizumab (RoActemra ®, EMA, 2016) in combination with methotrexate (MTX), is licensed for the treatment of severe, active and progressive rheumatoid arthritis (RA) in adults not previously treated with MTX and the treatment of moderate to severe active RA in adult patients who have either responded inadequately to, or who were intolerant to, previous therapy with one or more disease modifying anti-rheumatic drugs (DMARDs) or tumour necrosis factor (TNF) antagonists
- Tocilizumab is also licensed for the treatment of active systemic juvenile idiopathic arthritis (sJIA) in patients over 2 years, who have responded inadequately to previous therapy with NSAIDs and systemic corticosteroids. Tocilizumab can be given as monotherapy or in combination with MTX.
- NICE has not reviewed tocilizumab for use in Adult-onset Still's disease. It has published a technology appraisal guidance (TA238) recommending tocilizumab as a treatment for some children and young people with systemic juvenile idiopathic arthritis that is refractory to standard treatment (NICE, 2011).
- NICE (TAG375, 2016) has recommended tocilizumab in combination with methotrexate for treating RA if the disease activity score (DAS28) is greater than 5.1 and has not responded to intensive therapy with a combination of conventional DMARDs.

2. Summary of results

Anakinra

A total of five papers met the inclusion criteria determined on the basis of the research questions in the Population Intervention, Comparator, Outcomes (PICO). The papers varied significantly in the baseline characteristics of the patients included, the dosage and frequency of drug administration, the use of concurrent therapy and the previous therapies used by the patients. Patients in these studies were predominantly Group 2 (with systemic signs and symptoms and joint manifestations). The published studies have considered a relatively small cohort of patients and no systematic reviews were identified during the literature search. The majority of the studies reviewed were retrospective case series (Ortiz-Sanjuan et.al. 2015; Giampetro et.al. 2013; Lequerre et.al. 2008 and Laskari et.al. 2011) and these may be subject to bias in publication, reporting and selection and may not take account of all confounding factors. This may limit the generalisability of the study findings to a larger population.

One open label randomised multicentre study has been included that compares anakinra and Disease Modifying Anti-Rheumatic Drugs (DMARDs).

The main outcome measures reported were resolution of disease flares, reduction in steroid dose (steroid sparing) and clinical remission (defined as absence/reduction of fever, joint manifestations and lymphadenopathy along with normalisation or improvement in biochemical markers) (Ortiz-Sanjuan et.al. 2015; Giampetro et.al. 2013; Lequerre et.al. 2008, Laskari et.al. 2011). Two papers reported physician global assessment score and quality of life (Lequerre et.al. 2008; Laskari et.al. 2011).

Follow up varied from 12 months (Ortiz-Sanjuan et.al. 2015) to 27 months (Lequerre et.al. 2008). The studies with shorter follow up periods may not have had sufficient time to record medium to long term efficacy and safety of the drug. The studies evaluated some patients on anakinra as monotherapy and some where anakinra was given in combination with other drugs (for example methotrexate and/or prednisolone). However as results for all patients were pooled it is not possible to ascertain the specific effect of anakinra as monotherapy.

There appeared to be a greater improvement in systemic signs and symptoms after the introduction of anakinra compared to the improvement in joint manifestations (Ortiz-Sanjuan et.al.2015, Nordstrom et.al. 2012; Giampetro et.al. 2013, Laskari et.al. 2011, Lequerre et.al. 2008). Detail was not presented on response by AOSD sub-group and the majority of these patients were taking combination therapy.

Three studies (Ortiz-Sanjuan et.al. 2015, Lequerre et.al. 2008, Laskari et.al. 2011) reported statistically significant reductions in median corticosteroid dosage after anakinra administration. Anakinra was administered in combination with DMARDs. A statistically significant reduction in Erythrocyte Sedimentation Rate (ESR) and CRP was reported by Lequerre et.al. (2008) and Laskari et.al. (2011) and significant reduction in the mean number of swollen and tender joints was reported by Lequerre et.al (2008).

Adverse events varied in frequency and severity. The most commonly reported side effects were cutaneous reactions. These included rash (Ortiz-Sanjuan et.al (2015) n=8/41, Lequerre et.al (2008), n= 2/15, Laskari et al (2011) n=3/25), localised injection site reactions (one severity grade 1 and one severity grade 2 ISR requiring hospitalisation (Nordstrom et.al 2012, n=12), 2 severe ISRs (Giampetro et al (2013),n=28), Laskari et al (2011) n=5/25)

which in some cases lead to discontinuation of medication. Some patients discontinued their medication due to the severity of the rash ((n=2, Ortiz-Sanjuan et.al (2015))

Another commonly reported side effect was infection including urinary tract infections (UTIs), herpes zoster, pneumonia and varicella zoster (Ortiz-Sanjuan et.al (2015) (n=3/41, Laskari et al (2011) n=7/25, Rossi-Semerano et. al. (2015)).

Other side effects reported included single cases of other infections (for example bronchitis), hepatitis and hepatotoxicity.

There were no published studies evaluating the cost-effectiveness of anakinra and/or comparator therapies in the treatment of refractory adult-onset Still's disease.

Tocilizumab

A total of four papers met the inclusion criteria determined on the basis of the research questions in the Population Intervention, Comparator Outcomes (PICO). A case series published by Cipriani et.al. (2014) (n=11), a retrospective multi-centre open label study by Ortiz-Sanjuan et.al. (2014) (n=34), a prospective cohort study by Puechal et.al. (2011) (n=14) and a retrospective questionnaire based survey study by Elkayam et.al. (2014) (n=15). The papers varied significantly in the baseline characteristics of the patients included, the dosage and frequency of drug administration, the use of concurrent therapy and the previous therapies used by the patients. Patients in these studies were predominantly group 2. It was not possible to separate out the results for the two patient groups which makes it challenging to make specific recommendations for each sub-group of AOSD. While most studies state that patients had refractory disease their complete treatment history is not stated, so there may be patients included in the results who may not have had refractory disease.

There were no randomised controlled trials or systematic reviews identified in literature. The design of the studies mean they may be subject to selection, publication and reporting bias and may not take account of all confounding factors. This may limit the generalisability of the studies to a larger population.

The main outcome measures included were impact on systemic disease features (Cipriani et.al. 2014), reduction in inflammatory markers (Elkayam et.al. 2014) and steroid sparing (Ortuz-Sanjuan et.al. 2014, Elkayam et.al. 2014). The retrospective nature of some of the studies also limits the range of outcomes measured and reported.

Follow up varied from 6 months (Elkayam et.al. 2014 and Puechal et.al. 2011) to 12 months (Cipriani et.al. 2014 and Ortiz-Sanjuan et.al. 2014). The variability in the follow up duration means that long term efficacy and safety of tocilizumab cannot be fully evaluated. The studies evaluated some patients on tocilizumab as monotherapy and some for whom tocilizumab was given in combination with other drugs (for example prednisolone). However as results for all patients were pooled it is not possible to ascertain the specific effect of tocilizumab as monotherapy.

There appears to be evidence of effectiveness in the studies in modifying features of the disease such as reduction in median disease activity score, significant improvement in joint assessment ($P<0.05$) and VAS (Visual Analogue Scale) global assessment ($P<0.005$)

reported (Cipriani et.al. 2014). Of the 11 patients in this study 8 patients received Tocilizumab in combination with MTX and prednisolone and 3 had tocilizumab with prednisolone only. A statistically significant reduction in mean tender joints was reported by Elkayam et.al. (2014) ($P<0.05$). Other studies report on European League Against Rheumatism score (EULAR) remission (Cipriani et.al. 2014) (Puechal et.al. 2011) and substantial but not significant reduction in joint manifestations (Ortiz-Sanjuan, 2014). Detail was not presented on response by AOSD sub-group. Elkayam (2014) reports significant reduction in mean ESR and CRP values ($P<0.05$). Two studies reporting a statistically significant steroid sparing effect (Ortiz-Sanjuan et.al. 2014, and Elkayam et.al. 2014).

Adverse events varied in frequency and severity. The most commonly reported side effect was infection including upper respiratory tract infections (URTIs), herpes zoster, pneumonia and UTI (Ortiz-Sanjuan et.al (2014) (n=10/34), Cipriani et al (2014) n=1/11). In some cases this lead to patients discontinuing medication.

Another commonly reported side effect was injection site reaction (Cipriani et al (2014) n=2/11). Systemic flare was also reported (Cipriani et al (2014) n=3/11). Other side effects reported included single cases of hepatotoxicity.

There were no published studies evaluating the cost-effectiveness of tocilizumab and/or comparator therapies in the treatment of refractory adult-onset Still's disease.

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3. Methodology

- A description of the Population, Intervention, Comparison and Outcomes (PICO) document to assist with this review was prepared by clinical leads from NHS England and Public Health leads of the PWG (Policy Working Group).
- The following sources were searched for relevant publications: EMBASE, MEDLINE, CINAHL, Clinicaltrials.gov, NHS Evidence, Cochrane library and the National Institute for Health and Care Excellence (NICE) (section 11 includes search terms). National and international guidelines published were examined and referenced where relevant.
- The titles and abstracts of the results from the literature searches were assessed using the criteria included in the completed PICO template. Full text version of papers that appeared potentially useful in addressing the research questions were obtained and reviewed to determine whether they were appropriate for inclusion in this evidence review. Of the total 505 studies identified, 320 abstracts relevant to this topic were reviewed, 92 full papers were extracted and 9 full papers were selected for inclusion and are summarised in this review.
- Evidence with results were extracted from the selected papers and recorded in evidence summary tables (Table 7 below). Only outcomes specified in the PICO were extracted.
- All papers included in this review were assessed for their quality and graded using the Grading of Recommendations Assessment, Development and Evaluation criteria (GRADE) (Section 8).

4. Results

The evidence search identified a total of 320 abstracts relevant to the topic that were reviewed. 92 papers were extracted for further review and 9 papers that fulfilled the inclusion criteria to address the research questions in the PICO, were selected for inclusion (5 for anakinra and 4 for tocilizumab) which are summarised in this review. The studies selected for inclusion in this review were assessed on the basis of the criteria and research questions included in the PICO.

Anakinra

Five papers were identified that evaluated anakinra in refractory adult-onset Still's disease - an observational retrospective open label multicentre study by Ortiz-Sanjuan et.al. (2015), an open randomised multi-centre trial by Nordstrom et.al. (2012), a retrospective questionnaire based study by, Giampetro et.al. (2013), a retrospective questionnaire based study by Lequerre et.al. (2008) and a retrospective case series study by Laskari et.al. (2011). There were no systematic reviews or single or double blind trials comparing anakinra with the comparator therapies.

There were no studies of cost-effectiveness of anakinra for this patient population.

Clinical effectiveness

1. **Is anakinra a clinically effective treatment in patients with adult onset Stills disease (Group 1) whose symptoms and biochemical markers remain inadequately controlled after treatment with corticosteroids and methotrexate?**

In the retrospective open label multi-centre study by Ortiz-Sanjuan et.al (2015) 41 patients were prescribed anakinra (100mg as a daily subcutaneous injection). Patients received anakinra as a monotherapy (n=12) or combined with immunosuppressive drugs (n=29) - usually methotrexate. This study predominantly included group 2 patients (36 out of 41 patients had joint manifestations). After 1 year, the prevalence of joint manifestations decreased from 87.8% to 41.5%, cutaneous manifestations from 58.5% to 7.3%, fever from 78% to 22% and lymphadenopathy from 26.8% to 4.9%. No statistical testing was reported. The study reports reductions in the proportion of patients with abnormal elevation of CRP from 90.2% to 46.3%, ESR from 78% to 22% and reduction in abnormal elevation of ferritin levels from 63.4% to 36.6%. The proportion of patients with leucocytosis reduced from 65.9% to 14.6% and the proportion with anaemia reduced from 56.1% to 9.8%. No statistical testing was reported. Significant corticosteroid sparing effects were reported at 1 month, 3 months, 6 months and 12 months ($P<0.01$). The median prednisolone dosage of 20mg/day at baseline reduced to 5mg at the end of 1 year. While improvement in systemic symptoms has been reported, joint involvement was persistent in 41.5% of patients after 1 year. The independent effects of anakinra cannot be clearly established as combined results were presented for patients on both monotherapy and combination therapy. It was not possible to separate out the results for the two patient groups which makes it challenging to make specific recommendations for each sub-group of AOSD.

In the open randomised, multicentre study by Nordstrom et.al (2012) 12 patients were treated with anakinra (100mg subcutaneous injection daily) and 10 were treated with

DMARDs (6 on MTX, 2 on azathioprine (AZA), 2 on leflunomide (LEF)). All patients also received prednisolone (10mg/day) and NSAIDs if required. At baseline, patients presented with articular manifestations measured as tender joints (14% in DMARD group and 20% in anakinra group). Normalisation of CRP in both groups was reported by week 8. At week 24, 6 of the 12 patients given anakinra had achieved remission (defined as 8 weeks afebrile in the absence of NSAIDs, decrease in CRP and ferritin to reference limits and normal joint counts). 2 of the 10 patients on DMARDs achieved remission at the same time point. No statistical testing was reported to quantify this difference. By week 24, 3 patients on anakinra but none in the DMARD group were able to discontinue oral corticosteroids (P=0.22). More patients on anakinra than on DMARD achieved improvements in the SF36 physical health summary (P=0.011).

In the retrospective questionnaire based study by Giampetro et.al (2013) 28 patients were treated with anakinra (100mg/day). 19 of the 28 (68%) received anakinra in combination with MTX (dose ranging between 7.5 and 40mg/week), 1 patient received the drug in combination with hydroxychloroquine, 1 in combination with azathioprine (AZA) and 1 in combination with mycophenolate mofetil. 6 patients received anakinra as monotherapy. At 3 months, 15 of the 28 (54%) achieved remission and 9 of the 28 (32%) had achieved a partial response to treatment. 24 of the 28 patients (86%) were still being treated with anakinra at 3 months. 4 of the 6 patients on anakinra as a monotherapy achieved complete remission and 1 patient achieved partial remission. A mean prednisolone dose reduction from 34.4mg/day at time of introduction of anakinra to 7.9mg/day mg/day (n=15) was also reported. As most results were reported for the whole cohort it is difficult to establish a definitive effect of anakinra as monotherapy. At 23 months, 16 (57%) patients were still being treated with anakinra with 12 (42%) in complete remission. 4 (14%) patients showed a partial response with persistence of musculoskeletal symptoms. This was a small study with no statistical testing.

In the retrospective questionnaire based study by Lequerre et.al (2008) of the 15 patients studied, 11 were administered anakinra in combination with MTX or another DMARD (1 with rituximab and 1 with cyclophosphamide). 10 patients had chronic arthritic disease with systemic flares, 3 had systemic disease and 2 showed no systemic symptoms but active articular involvement. At 3 months, 11 (73%) patients reported improvement in clinical and biological disease markers. ESR reduced from 74mm/h to 22.1mm/h (P=0.0005), CRP reduced from 91.9mg/l to 16.6mg/l (P=0.001), leucocyte count (10^9/l) reduced from 11.9 to 7.5 (P=0.017). There was also significant improvement in joint manifestations - mean tender joint count reduced from 8.5 to 1.5 (P=0.0002) and mean swollen joints reduced from 5.9 to 0.9 (P=0.0005). Significant steroid sparing was reported with mean prednisolone reduction from 26.8mg/d to 8.6mg/d (P=0.0047). A significant reduction in physician global assessment of disease activity was also reported reducing from 6.9 to 2 (P=0.002). Due to the pooled results it is difficult to determine which AOSD sub-group could most benefit. This was a small retrospective questionnaire that relies on the accuracy, availability of data and recall of the physician completing the questions. As anakinra was administered with other drugs it is difficult to ascertain the specific effect of anakinra on disease parameters.

In the retrospective case series study by Laskari et.al (2011) with predominantly group 2 patients (88% with arthralgias) 16 of the 25 patients received anakinra (100mg/day subcutaneously) in combination with a DMARD (MTX in 13, Leflunomide in 1, cyclophosphamide in 1). 9 patients received anakinra as monotherapy. 21 of the 25 (84%) achieved a complete resolution of disease activity at 12 months, 3 (12%) patients achieved a partial response and 1 showed no response. At 3 months, significant improvement of clinical features (fever, rash, lymphadenopathy, hepatosplenomegaly) was reported (P<0.001). There was a significant reduction in CRP (mg/dl) from 111mg/dl at baseline to 6mg/dl at month 3 (P=0.028) and ESR from 75mm/h to 10mm/h (P=0.04) at

month 3. High ferritin levels (>300ng/ml) were reported in 24 patients at baseline and 4 patients at month 1 (P=0.004). There was a reduction in the number of patients with anaemia (Hb<12 for females and <13.5 for males) from 16 patients at baseline to 5 patients at 3 months (P=0.008). The number of patients with leucocytosis (>10000/mm3) reduced from 21 patients at baseline to 9 patients at month 1 (P=0.001). The VAS global score reduced from 2.25 at baseline to 0.3 at month 1 (P<0.001). A significant reduction in methylprednisolone oral dose was reported at month 1 (14 mg/day, P=0.001) and month 3 (8mg/day, P=0.001) compared to baseline (18 mg/day). This study considered a small mixed cohort of patients and did not differentiate the results for patients treated with anakinra as monotherapy and those who received it as a combination therapy.

2. **Is anakinra more effective than comparison therapies (methotrexate and/or corticosteroids and/or other DMARDs and Canakinumab for group 1 and Etanercept for group 2) in achieving the critical and important outcomes for patients as outlined in the PICO?**

There were no randomised control trials comparing anakinra with other therapies to provide direct comparison of clinical effectiveness so judgements on relative safety and efficacy will be limited.

However the study by Nordstrom et.al (2012) did allow comparison between anakinra and DMARDs. 12 patients were treated with anakinra (100mg subcutaneous injection daily) and 10 were treated with DMARDs (6 on MTX, 2 on azathioprine (AZA), 2 on leflunomide (LEF)). All patients also received prednisolone (10mg/day) and NSAIDs if required. At baseline, patients presented with articular manifestations measured as tender joints (14% in DMARD group and 20% in anakinra group). Normalisation of CRP in both groups was reported by week 8. At week 24, 6 of the 12 patients given anakinra had achieved remission (defined as 8 weeks afebrile in the absence of NSAIDs, decrease in CRP and ferritin to reference limits and normal joint counts). 2 of the 10 patients on DMARDs achieved remission at the same time point. No statistical testing was reported to quantify this difference. By week 24, 3 patients on anakinra but none in the DMARD group were able to discontinue oral corticosteroids (P=0.22). More patients on anakinra than on DMARD achieved improvements in the SF36 physical health summary (P=0.011).

3. **Is anakinra a cost effective treatment in patients with adult onset Stills disease (Group 1) whose symptoms and biochemical markers remain inadequately controlled after treatment with corticosteroids and methotrexate?**

There is no evidence on cost-effectiveness of anakinra and/or comparator therapies in the treatment of refractory Adult-onset Still's disease.

4. **Is anakinra more cost effective than comparison therapies?**

There is no evidence on cost-effectiveness of anakinra and/or comparator therapies in the treatment of refractory Adult-onset Still's disease.

5. **Is anakinra a safe treatment for patients with adult onset Stills disease (Group 1) whose symptoms and biochemical markers remain inadequately controlled after treatment with corticosteroids and methotrexate?**

The patient populations in the studies reviewed were in Group 1 and Group 2 and the majority of results presented were pooled. Therefore, it is not possible to define adverse events specific to either AOSD sub-group.

In the study by Ortiz-Sanjuan et.al (2015) (n=41), cutaneous reactions were the most common complication (n=8) with 2 patients discontinuing treatment due to the severity of the rash. 2 patients reported urinary tract infections (UTIs), and 1 reported a herpes zoster infection. Two patients discontinued their medication due to severe infections. In the study by Nordstrom et.al (2012) (n=12) 1 patient experienced worsening of disease, 7 patients reported grade 1 ISRs and 1 reported a grade 2 ISR. In the study by Giampetro et.al (2013) (n=28), at 23 months 4 patients reported a disease flare and 2 discontinued treatment due to a severe ISR. Lequerre et.al (2008) reported 2 out of 15 patients developing a severe skin rash leading to withdrawal of anakinra. Other side effects reported included singe cases of other infections (for example bronchitis and uncomplicated hepatitis A). One patient reported osteonecrosis but this may have been a side effect of long term corticosteroid treatment. In the study by Laskari et.al (2011) (n=25) 3 patients developed a severe urticarial reaction and discontinued therapy, 7 (28%) patients developed infections and 5 developed local hypersensitivity at the injection site.

In a review on tolerance and efficacy of off-label anti-interleukin-1 treatments in France, Rossi-Semerano et. al. (2015) reported serious adverse events in 3 patients treated with anakinra for AOSD. One patient developed pneumonia, one developed a varicella zoster infection and one developed macrophage activation syndrome. In a review of five studies by Hong et.al. (2014), a severe urticarial reaction was the most common adverse event recorded which led to withdrawal of anakinra in some cases.

Ahmed et al. (2015) have published a case report of anakinra associated hepatotoxicity in a 46 year old woman which resolved after discontinuation. Aly et.al (2013) also reported subacute liver failure associated with anakinra treatment for AOSD. Meyer et.al. (2012) reported acute hepatitis in 3 female patients with AOSD with normalisation of liver enzymes after withdrawal of anakinra. A case report by Taylor et. al. (2016) reported a case of an adolescent male with AOSD with acute liver failure which developed shortly after initiation of anakinra and improved after withdrawal of the drug. There was insufficient clinical information in these studies to ascertain whether these patients were receiving anakinra for refractory AOSD.

Pregnancy

The license for anakinra states that there is limited data on the use of anakinra in pregnant women (EMEA). Reproductive studies on rats and rabbits have revealed no evidence of impaired fertility or harm to the foetus. There is limited anecdotal experience on the use of anakinra in pregnancy. The license states that anakinra is not recommended for use during pregnancy, while breast feeding and in women of child bearing age not using contraception.

The guideline published by Flint et. al. (2016) states that there is limited evidence on which to base a recommendation relating to the use of anakinra in pregnancy, during breastfeeding or related to paternal exposure but suggests that unintentional exposure in the first trimester is unlikely to be harmful.

Tocilizumab

4 papers evaluating tocilizumab in refractory AOSD were included in this review. These include a case series by Cipriani et.al. (2014), a retrospective multi-centre open label study by Ortiz-Sanjuan et. al. (2014), a prospective cohort study by Puechal et.al. (2011) and a retrospective questionnaire based survey study by Elkayam et.al. (2014). There were no systematic reviews or single or double blind trials identified comparing the effect of tocilizumab with comparator therapies.

1. **Is tocilizumab a clinically effective treatment in patients with adult onset Stills disease (Group 1) whose symptoms and biochemical markers remain inadequately controlled after treatment with corticosteroids and methotrexate and anakinra?**

In the studies reviewed, the patient cohort includes patients with systemic (Group 1) and articular disease (Group 2). No studies directly reported the effect of tocilizumab exclusively in patients with systemic type AOSD (Group 1) refractory to corticosteroids, MTX and anakinra. As many of the results presented were pooled it is not possible to ascertain which group will most benefit from the use of tocilizumab.

2. **Is tocilizumab a clinically effective treatment in patients with adult onset Stills disease (Group 2) whose symptoms and biochemical markers remain inadequately controlled after treatment with corticosteroids and methotrexate?**

In the case series by Cipriani et.al (2014), 11 patients were treated with tocilizumab (8mg/kg every 4 weeks for 12 months). 8 of these patients received tocilizumab in combination with MTX and prednisolone and 3 patients received tocilizumab with prednisolone without MTX. All patients had chronic arthritis (Group 2). There was a reduction in median disease activity score in 28 joints - reducing from 5.62 at baseline to 1.61 at month 12. EULAR remission was observed in 45.45% (5/11) of patients at 3 months and in 81% (9/11) at 12 months. Remission of fever and systemic symptoms was reported in all patients, however no statistical testing was reported. A statistically significant improvement in joint assessment was reported after 6 months and 12 months of treatment compared to baseline ($P<0.05$). Reduction in ESR, CRP and ferritin values was reported at month 3 and remained stable at month 12. There was also improvement in haemoglobin levels at month 12 in 4 patients but no statistical testing was reported. A significant improvement in median patient VAS (Visual Analogue Scale) score was reported, reducing from 75 at baseline to 0 at month 12 ($P=<0.005$). Prednisolone was tapered from baseline 50mg/day to 6.25mg/day at month 6 with 8 of the 11 patients (72%) discontinuing corticosteroid therapy after 12 months. This small case series (n=11) does not allow estimation of the precise effects of tocilizumab as monotherapy as all patients received the drug in combination.

In the retrospective multi-centre open label study by Ortiz-Sanjuan et.al (2014) 34 patients were treated with tocilizumab (8mg/kg) but in variable doses and frequencies (every 4 weeks (n=22), every 2 weeks (n=10) and 4mg/kg every 4 weeks (n=2)). 15 patients received tocilizumab as monotherapy and 19 in combination with MTX. Patients were predominantly diagnosed with Group 2 AOSD. After 1 year, the prevalence of joint manifestations in the patient group decreased from 97.1% to 32.4%. There was also a reduction in the prevalence of fever (from 78% to 22%), lymphadenopathy (from 29.4% to 0%) and rapid improvement of other systemic symptoms such as cutaneous

manifestations. No statistical testing was reported for these parameters. 32.4% patients still had persistent joint involvement after 1 year of tocilizumab therapy. Reduction in ESR, CRP, ferritin levels, leucocytosis and anaemia was reported but did not reach statistical significance. A significant steroid sparing effect (P<0.05) was reported with median prednisolone reducing from 13.8mg/day at baseline to 2.5mg/day at 1 year. However the specific effect of tocilizumab as monotherapy cannot be ascertained as the drug was given as a combination therapy. There may be a greater clinical effect on joint manifestations of AOSD compared to systemic manifestations, but this is based on a small number of patients (n=34).

In a prospective cohort study by Puechal et.al (2011) 14 patients with AOSD received tocilizumab at different doses and frequencies ((n=9) 8mg/kg every 4 weeks, 8mg/kg every 2 weeks (n=4) and 5mg/kg monthly (n=1)). Tocilizumab was given in combination with other drugs ((n=8) MTX, (n=2) LEF). 4 patients received tocilizumab monotherapy. 8 of the 11 patients had the chronic arthritic form of the disease. Of the 11 patients who successfully completed treatment in this 6 month study, resolution of systemic symptoms (fever and eruption) was observed in 6 patients. Reduction in mean DAS28, good EULAR response (n=9) and EULAR remission (n=8) at 6 months were also reported. Reduction in median ESR (from 36.5mm/h to 12.5 at month 6), CRP (from 5.2 at baseline to 0.6 at month 6), serum ferritin (from 1939ng/ml to 209 at month 6) and leucocyte count (from 10.65 at baseline to 9.03 at month 6) were reported but with no statistical significance reported. Prednisolone dosage reduced to a mean of 13mg/day at 3 months to 10.3mg/day at 6 months, however no correlation was found between the tocilizumab dose and achievement of arthritis or systemic remission or with the decrease of corticosteroids.

In the retrospective questionnaire based survey study by Elkayam et.al (2014) (n=15) all patients had arthralgia with fever and/or rash. Patients received varying doses and frequencies of tocilizumab (n=12 patients received tocilizumab 8mg/kg/month, n=3 received 8mg/kg twice a month). After 6 months, there was a significant reduction in mean tender joints (P<0.05) reported with resolution of systemic symptoms in 86% patients after 6 months of treatment. EULAR response was 57% after 6 months with a reported regression of amyloidosis. Mean ESR reduced from 60mm/h to 3.9, CRP reduced from 11.6 to 0.5 (P<0.05) and significant steroid sparing was reported (P<0.05) with mean prednisolone dose reduced from 27.6mg/d to 4.9mg/d. This study is a retrospective survey with limitations around data completeness as some of the rheumatologists surveyed had incomplete treatment histories for their patients.

3. Is tocilizumab more effective than comparison therapies in achieving the critical and important outcomes for patients as detailed in the PICO form?

There were no head to head comparison or single or double blind trials comparing tocilizumab with other therapies, therefore it is difficult to a make direct comparison of clinical effectiveness compared to standard therapy.

4. Is tocilizumab a cost effective treatment in patients with adult onset Stills disease (Group 1) whose symptoms and biochemical markers remain inadequately controlled after treatment with corticosteroids and methotrexate and anakinra?

There were no studies identified that provided information on the cost effectiveness of tocilizumab in the treatment of refractory Adult-onset Still's disease (Group 1).

5. **Is tocilizumab a cost effective treatment in patients with adult onset Stills disease (Group 2) whose symptoms and biochemical markers remain inadequately controlled after treatment with corticosteroids and methotrexate?**

There were no studies identified that provided information on the cost effectiveness of tocilizumab in the treatment of refractory Adult-onset Still's disease (Group 2).

6. **Is tocilizumab more cost effective than comparison therapies?**

There were no studies identified that evaluated the cost effectiveness of tocilizumab compared to comparison therapies in the treatment of refractory Adult-onset Still's disease.

7. **Is tocilizumab a safe treatment for patients with adult onset Stills disease (Group 1) whose symptoms and biochemical markers remain inadequately controlled after treatment with corticosteroids and methotrexate and anakinra?**

The patient populations in the studies consisted of patients with AOSD who had systemic and chronic articular manifestations of the disease. Therefore it is not possible to define adverse events specific to either AOSD sub-group.

8. **Is tocilizumab a safe treatment for patients with adult onset Stills disease (Group 2) whose symptoms and biochemical markers remain inadequately controlled after treatment with corticosteroids and methotrexate?**

Tocilizumab is licensed by the European Medicines Agency to treat rheumatoid arthritis and the most common side effects are reported as upper respiratory tract infections, hypertension and abnormal liver function tests. Serious potential side effects include infections, diverticulitis and hypersensitivity.

The adverse events associated with the use of tocilizumab in refractory AOSD include infections, elevated hepatic enzymes, leukopenia, neutropenia, hypercholesterolaemia and systemic/arthritic flares.

In the study by Cipriani et.al. (2014) 3 out of 11 patients (Group 2) experienced adverse events such as tender and swollen joints, onset of systemic symptoms and a worsening of patient VAS global health score with high ESR, CRP and ferritin. Minor adverse events reported include one upper respiratory tract infection (URTI) and 2 ISRs after one infusion. In the study by Ortiz-Sanjuan et.al. (2014), after a median follow up of 19 months, 10 out of 34 patients experienced a range of infections (1 pyelonephritis and acute enterocolitis, 1 bacterial spondylodiscitis, 1 pneumonia, 3 URTI, 1 dental infection, 1 urinary infection, 1 Epstein-Barr infection and 1 herpes zoster infection). 2 patients had infections that lead to discontinuation of treatment. Puechal et. al. (2011) (n=14)

described adverse events that included necrotising angiodermatitis (n=1), chest pain (n=1) and ongoing episodes of high fever (n=1).

In a case report by Drepper et. al. (2013), tocilizumab induced liver injury was reported 19 months after initial tocilizumab exposure as a rare event in an 18 year old patient. In another case report by Tsurukawa et.al. (2016), a herpes zoster infection occurred five days after an infusion in a 56 year old patient however the patient was also on immunosuppressive therapy so this may be a case of an atypical opportunistic infection. In these two case reports there is insufficient clinical detail to ascertain if the patients had refractory AOSD.

Pregnancy and breast feeding

The license information states that there is not adequate data for the use of tocilizumab in pregnant women and studies in animals have shown an increased risk of spontaneous abortion/foetal death. It is also not known if tocilizumab is excreted in human breast milk. Women of child bearing potential must use effective contraception during and up to 3 months after treatment. A review by Calligaro et. al. (2014) on safety of biological drugs in pregnancy recommended that tocilizumab is discontinued at least 3 months prior to conception. This review reported on two case series (n = 39 outcomes of pregnancies exposed to tocilizumab) with 41% live births, 20.5% spontaneous abortion and 33.3% elective terminations.

9. **What is the incidence of adult onset Stills disease overall and Groups 1 and 2 in the English population?**

There is no consensus on the incidence and prevalence of AOSD. Fautrel et al (2004) states the estimated incidence of AOSD in France is between 1 – 2 cases per million population per year. Therefore, it can be estimated that in England, approximately 55-110 new cases of Adult-onset Still's disease could be expected every year. This makes assumptions about the similarities of the French and English populations. There is insufficient epidemiological information to make estimates of incidence for each AOSD sub-group.

10. **What is the prevalence of adult onset Stills disease overall and Groups 1 and 2 in the English population?**

Fautrel (2004) reports the prevalence of adult-onset Still's disease at around 10 per million (range 7.3 to 14.7) in Japan. Asanuma et.al (2015) estimated the prevalence of adult-onset Still's disease at 3.9 per 100,000 in a Japanese study. Based on extrapolated estimates for England, approximately 600-800 cases of adult-onset Still's disease could be estimated to be prevalent in the population. Applying this epidemiology should be interpreted with caution given the significant differences in the ethnic and age profiles between the Japanese and English populations. There is insufficient epidemiological information to make estimates of prevalence for each AOSD sub-group.

Discussion

The evidence search identified a total of 320 abstracts relevant to the topic that were reviewed. 92 papers were extracted for further review and 9 papers that fulfilled the inclusion criteria to address the research questions in the PICO, were selected for inclusion (5 for anakinra and 4 for tocilizumab) which are summarised in this review. The studies selected for inclusion in this review were assessed on the basis of the criteria and research questions included in the PICO.

The majority of the studies included are retrospective case series which were not controlled and were not randomised. They included small numbers of patients. Due to the nature of the study design the evidence is of poor to moderate quality. Most studies did not directly compare anakinra or tocilizumab with standard therapy so judgements on relative efficacy and safety will be limited.

The baseline characteristics of patients differed in terms of AOSD sub-group, previous treatment and severity of symptoms. The length of follow up also varied. The studies with shorter follow up may not have had sufficient time to record the medium and longer term effects of the drugs or their side effects.

In the majority of studies, the anakinra or tocilizumab was administered in combination with other drugs with only a minority of patients receiving it as a monotherapy. Most studies analysed these patients together and therefore outcomes could not be split by baseline characteristics, AOSD sub-group or treatment type. For patients on combination therapy it is difficult to ascertain the specific effect of tocilizumab or anakinra.

Patients treated with anakinra and tocilizumab appeared to show some efficacy in relief of systemic features of the disease. There was a lesser effect on the articular manifestations of AOSD. Patients treated with the drugs also reported significant steroid sparing and improvement in biochemical markers and VAS scores. Many studies did not undertake statistical testing to describe the impact of the changes observed. Therefore the degree of effectiveness cannot be reliably quantified using the available evidence.

Significant adverse events have been reported with use of anakinra and tocilizumab which has led to discontinuation of treatment in some patients.

5. Conclusion

The published evidence on the clinical efficacy and safety of both anakinra and tocilizumab in AOSD consists of case series, retrospective studies, a randomised open label study and a prospective cohort study. These studies are of variable quality. The major drawback of these studies is that they are subject to selection bias and the effect of confounding factors so it is difficult to understand the true efficacy of the intervention.

The evidence suggests that both anakinra and tocilizumab are associated with a positive impact on biochemical markers, systemic features and use of steroids in patients with refractory AOSD. However as both drugs were administered as both monotherapy and combination therapy their exact effect cannot be ascertained. As patients received different drugs in combination with anakinra and tocilizumab it is not possible to make clear recommendations on which drugs could be given in combination or at which stage of disease progression. Patients who received the drug were from Group 1 and 2 but pooled results were presented so it is not clear which group would most benefit from the therapy.

Adverse events were reported relatively frequently and ranged from injection site reactions to severe infections. The lack of randomised controlled trials may be due to the rarity of the disease and heterogeneous presentations which means it is difficult to make direct comparisons with standard care.

No studies have evaluated the cost-effectiveness of either drug or compared its cost effectiveness with existing treatments.

6. Evidence summary table

Use of Anakinra to treat Adult-onset Still's disease refractory to MTX, corticosteroids									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
Ortiz-Sanjuan et.al. Ta	Observational study – Retrospective open label multi-centre study	41 patients (26 women/15 men) Mean age 34.4 (+/- 14 years) Median Adult-onset Still's disease duration – 3.5years(2-6yrs) Refractory to synthetic immunosuppressive drugs and in some cases to 1 biologic agent Group 2 predominantly (n=36) Joint	Anakinra prescribed as monotherapy (n=12) or combined with synthetic immunosuppressive drugs (n=29), usually methotrexate Initial anakinra dose = 100mg/day in all 41 pts as subcutaneous daily injection After 1 year 100mg/da- 22 pts (53.7%) 100mg/48 hrs - 3 (7.3%) 100mg/72 hrs - 1 (2.4%) 100mg/2w – 1 (2.4%) Mean follow	**Primary outcome – Clinical effectiveness** **Secondary outcome – safety**	**Response to treatment/Resolution of disease flares/clinical remission e.g. joint manifestations, fever, rash, splenomegaly, lymphadenopathy, hepatomegaly, pericarditis and pleuritis** = **Frequency of further disease flares** **Adverse treatment effects**	After 1 year frequency reductions noted were - joint manifestations - decreased from 87.8% to 41.5% -Cutaneous manifestations - 58.5% to 7.3% -Fever decreased from - 78% to 22% -Lymphadenopathy decreased from - 26.8% to 4.9% 41.5% had persistence of joint involvement after 1 year After median follow up of 16 months cutaneous reactions were most common complications (n=8). 2 out of 8 discontinued due to severe rash. Clinical improvement followed after anakinra discontinuation	7	Directly applicable but note small cohort size	Due to the refractory nature of the disease the prior history of treatment in all patients is limited. There may be an absence of data on potential confounding factors. It is not possible to determine the specific effects of anakinra as monotherapy since anakinra was prescribed in combination with other drugs and pooled results are presented for the entire patient cohort. Patients were predominantly Group 2 type but as there was no sub-group analysis the effect of anakinra on different groups of AOSD cannot be determined. Patients are followed up to 1 year so long term efficacy and safety cannot be ascertained from the findings. Results do not include statistical significance except for the steroid sparing effects [P<0.05] and there is no information on cost-effectiveness or physician's global assessment which limits the interpretation of findings.

		manifestation 87.8%, fever 78%, cutaneous rash 58.5%	up = 16 months Concomitant Rx with anakinra at baseline = Corticosteroids – 40(97.6%) MTX – 24(58.5%) HCQ – 1 (2.4%) Immunosuppressive Rx before anakinra comprised of non-biologic agents- MTX(32), LFN(7), CsA(4), CPM(2), SZP(1), MMF(1) and Biologic agents - ETN(10), ADA(6) IFX(9), Tocilizumab(1)	**Primary outcome – clinical effectiveness** **Primary outcome – clinical effectiveness** **Secondary outcome –**	**Normalisation/improvement of ESR and/or CRP and/or ferritin** --- **Normalisation/improvement of anaemia and leucocytosis** -- **Dosage of prednisolone and DMARDs** **Adherence to treatment**	-6(14.6%) with mild local cutaneous reactions in the site of anakinra injection -Severe infections = 2 (therapy discontinued) UTI=2, Herpes Zoster=1, Mild leukopenia =3, Myopathy with elevation of muscle enzymes=1 Frequency of abnormal elevation of CRP down – 90.2% to 46.3%; ESR down – 78% to 22% -High serum ferritin levels down from 63.4% to 36.6% of pts Leucocytosis – 65.9% to 14.6%Anaemia 56.1% to 9.8% anakinra allowed significant steroid sparing effects (P=<0.05) from median Prednisolone 20mg/day at baseline to 5mg at 1 year After 1 year 14 pts (34%) discontinued biologic agent because of remission			

						(1), side effects (n=5), lack of efficacy (n=7), desire to become pregnant (m=1)			
Giampetro et.al. 2013	Retrospective study (Data collected using a standardised questionnaire) Groups 1 & 2	28 Adult-onset Still's disease patients (diagnosed using Yamaguchi criteria) from 9 different rheumatology or int medicine depts. In France included from a national survey among all depts. of rheumatology and internal medicine in France - To retrospectively assess the long-term efficacy and safety of anakinra in Adult-onset Still's disease. Mean SD	anakinra 100mg daily administered subcutaneously, alone or in combination with MTX. 19 (68%) treated with ANA in assoc with MTX (avg dose – 17.2mg/week – range 7.5-40mg / week) 1 treated with hydroxychloroquine, 1 with azathioprine and 1 with mycophenolate mofetil. 6 (21%) were not receiving a DMARD and ANA was used as monotherapy. all except 1 pt were cortico-dependent with dependence threshold of 11mg/day	**Primary outcome – clinical effectiveness** **Secondary outcome – safety**	**Response to treatment/Resolution of disease flares/clinical remission e.g. joint manifestations, fever, rash, splenomegaly, lymphadenopathy, hepatomegaly, pericarditis and pleuritis –** **Adverse treatment effects –**	Serositis (pericarditis, pleuritis) – 0 all patients experience clinical significant rseponse to ANA. At 3 months – 15 (54%) achieved remission. 24 (86%) were still being treated with ANA. 9(32%) had a partial response with arthritis and myalgia as persisting symptoms. 1 patient – liver enzymes remained elevated 4 out of 6 who had ANA as monotherapy achieved complete remission and 1 partial remission. At 23 months, 12 (43%) discontinued ANA, 2 due a partial response, 4 due to an Adult-onset Still's disease flare after a period of complete remission (mean duration of remission 13.8 months), 2 due to side effects (severely itchy skin rash at site	6	Directly applicable but note small cohort size	This is a retrospective questionnaire based study and available data on results and outcomes is likely to be limited due to the design of this study. Confounding bias is more common in retrospective studies as interpretation is based on available information. In this study, the results are not tested for statistical significance. The specific impact on the two types of AOSD cannot be determined as results are pooled. The patient cohort is small and follow up is restricted to 23 months which may limit the generalisability of findings and understanding of long term efficacy and safety of treatment with anakinra in refractory AOSD patients. Effects of anakinra as monotherapy cannot be ascertained as it is used in combination with MTX and the results are pooled for the entire cohort. Overall anakinra dose tapering or discontinuation is seen to be associated with relapse in half of the patients suggesting continued long term administration may be required to sustain effects on clinical and biochemical markers.

		age – 40.3 years (range 23-72 years) Mean SD disease duration – 9.3 years (range 1-22 yrs) Ratio of Men to women 1:2 (M-9, F-19) 13 patients – Predominantly articular disease and systemic in others. all patients refractory to conventional therapy – NSAIDs, CTX, DMARDs. 14 failed other biologic agents (11 Etanercept, 9 infliximab, 3 adalimumab and 2 rituximab) Previous therapeutic failure – Prednisolon	prednisolone or equivalent	**Primary outcome – clinical effectiveness** **Secondary outcome** **Secondary outcome**	**Normalisation/improvement of ESR and/or CRP and/or ferritin -** **Normalisation/improvement of anaemia and leucocytosis** **Dosage of prednisolone and DMARDs** **Adherence to treatment**	of injection despite a significant response of Adult-onset Still's disease. Rash at injection site rated as mild in all patients affected. Treatment discontinued in 2 patients with no severe infection. ESR mean – 14.6mm/hr CRP mean – 15.19mg/dl High neutrophil count – 14(50%) Neutrophil count mean – 7810(4300 – 14,400) MTX dose reduction was possible in 3 patients (1%), Avg dose reduction – 5mg/week. Prednisolone mean decreased from mean 34.4 mg/day to 9.7mg/day. 2 patients (22%) discontinued MTX without an observed relapse. 2 discontinued due to side effects, 3 due to remission, 1 due to procreation			

		e(28), MTX(25), Other(5), IVIg(8) Cyclophosphamide(2), Anti-TNFalpha(23), Rituximab(2)				desire, 2 due to unsatisfactory response and 4 due to loss of efficacy after a period of complete remission. 6(21%) experienced reduction in ANA doses with maintained remission in 2 patients and relapse in others Some patients experienced a progressive reduction of doses from 7,6,5, and 4 to finally 3 injections/week 4 patients relapsed when switching from daily to every other day injections. Complete discontinuation was in 6 patients who achieved remission			
Lequerre T et.al. 2008	Retrospective questionnaire based study in France Data collection via standard online questionnaire in	15 AOSD patients 4 – Male 11 – Female Mean age – 38.1 (SD-12.8) Mean disease duration – 7.8(SD-6.4) Systemic features – 13 (87%) Fever – 13(87%)	Anakinra 100mg/day 12 patients were on steroid treatment at the start of anakinra treatment. 11 out of 14 patients were administered anakinra in combination	**Primary outcome – clinical effectiveness**	**Response to treatment/Resolution of disease flares/clinical remission e.g. joint manifestations, fever, rash, splenomegaly, lymphadenopathy, hepatomegaly, pericarditis and pleuritis**	11 out of 15 (73%) patients had improvement in all disease markers and were still on treatment. Clinical and biological markers improved in 9 of 15 (60%) patients by at least 50% at 6 months. 11 patients responded to anakinra. 9 of 11 achieved complete response at 3 months;	5	Directly applicable but note limitations and small cohort size	This is a retrospective online questionnaire based survey study. The results for adult-onset Still's disease patients (n=15) treated with anakinra are provided separately. It is difficult to assess the effects of anakinra as monotherapy as it is used in combination with MTX or another DMARD in 11 patients. Effects of anakinra on patients with predominantly systemic (Group1) disease and those with chronic articular manifestations along with systemic features (Group 2) cannot be ascertained as the results are pooled for the entire cohort of 15 patients. The results show significant steroid sparing (P=0.0047) in patients after administering anakinra with significant improvement in biochemical markers (ESR P=0.0005, CRP P=0.001) and reduction in mean tender and swollen joints (P=0.0002 and P=0.0005]. The patient cohort is small which may limit the generalisability of findings.

	France	Rash – 8(53%) Serositis – 2 (13%) 10 patients had chronic arthritic form with systemic flares, 3 had systemic form and 2 showed no systemic symptoms but an active articular involvement Previous DMARD – MTX treatment – 15(100%) Ongoing prednisolone daily – 26.8mg	with MTX or another DMARD (n=2) Data was analysed retrospectively at 3 months, 6 months and last follow up ranging from 11 to 27 months Response was defined as resolution of systemic symptoms and an improvement of the American College of Rheumatology (ACR) score by at least 20%.	**Secondary outcome – safety**	**Adverse treatment effects –**	10 of 11 at 6 months; and 9 of 11 at last follow-up (ranging from 11-27 months) 2 patients had partial response at the last follow up At last follow up -Mean tender joint count reduced from 8.5(SD-5.9) to 1.5(SD-2.7) [P=0.0002] -Mean swollen joint count reduced from 5.9(SD-5.8) to 0.9(SD-1.5) [P=0.0005] 4 patients stopped; 2 due to lack of efficacy and 2 due to side effects. Local pain was recorded in 1 patients. 2 patients developed skin rash after 1 month and 3 months leading to withdrawal of anakinra. In other patients, 1 patient had bronchitis, one uncomplicated hepatitis A, one varicella and one cutaneous infection. 1 patient had osteonecrosis of femoral hip, possibly			

						due to long lasting corticosteroid treatment			
				Primary outcome – clinical effectiveness	**Normalisation/improvement of ESR and/or CRP and/or ferritin -**	2 patients had a partial response (displaying fever or elevated ESR or CRP) ESR reduced from 74mm/h (SD-33.5) to 22.1 (SD-24.6) (P=0.0005) CRP reduced from 91.9 (SD-71.8) to 16.6(SD-20.6) [P=0.001] Ferritinaemia (ng/ml) reduced from 997 (SD-1410) to 283(SD-419) [P=0.094]			
				Primary outcome - efficacy	**Normalisation/improvement of anaemia and leucocytosis**	Leucocyte count reduced from 11.9 (SD-6.1) to 7.5 (SD-2.3)[P=0.017]			
				Secondary outcome	**Dosage of prednisolone and DMARDs**	Corticosteroids stopped in 2 of 11 patients who responded and dose reduced in by 45% to 95% in relation to baseline in 8 patients. Mean dose of prednisolone reduced from 26.8mg/d to			

						8.6mg/d at last follow up [P=0.0047] 7 of 12 AOSD patients continued methotrexate. Of these 12 patients 9 achieved clinical remission			
				Primary outcome **Primary outcome**	**Important to decision-making:** **Physician global assessment of disease activity (PGA)** **Subjective symptom scores –**	Physician global assessment of disease activity (0-10 VAS) – reduced from 6.9(SD-2) to 2(SD-2.3) [P=0.002] Assessment of pain (0-10VAS) – reduced from 6.6 (SD-2.2) to 1.8(SD-2.5) [P=0.0002]			
Laskari et.al. 2011	A retrospective case series – study Retrospective study using medical records of patients followed by final evaluation by	25 patients over 18 years of age (4 with juvenile onset and 21 adolescent or adult onset disease) Male – 13 Female – 12 Median age – 32 (18-71)	16 out of 25 patients received - anakinra 100mg/day subcutaneously as adjunct therapy with a DMARD; 9 patients received anakinra as monotherapy Concomitant	**Primary outcome – clinical effectiveness**	**Response to treatment/Resolution of disease flares/clinical remission e.g. joint manifestations, fever, rash, splenomegaly, lymphadenopathy, hepatomegaly, pericarditis and pleuritis –**	21 out of 25 patients (84%) with complete resolution of clinical activity. 3 (12%) had partial response (presented with arthralgia (n=2) or arthritis and intermittent fever (n=1). 1 patient showed not response after 4 months and was assigned to another treatment. At 3 months significant	6	Directly applicable but note limitations and small cohort size	This retrospective case series study of 25 patients is limited by having to rely on patient data available from medical records with incomplete information on drugs used before initiating therapy with anakinra. This may lead to confounding bias while interpreting results. The study includes a small cohort of patients and more than a third of patients had a follow up of less than a year which may not give time to ascertain the medium and long term efficacy or safety of the drug. The study states that a median of only 6 patients (5-8) fulfilled Yamaguchi criteria. The refractory status of patients is based on resistance to corticosteroids, DMARD or TNF inhibitors, so it is not possible to establish if all patients were refractory to corticosteroids and MTX before commencing anakinra. While this study does not present the results separately for patients with anakinra as monotherapy or combined with a DMARD, this is the

	physician contacting patient to estimate exact time points of partial and complete response and relapse.	Median disease duration – 7 months (1-228) Medicipran No. of Yamaguchi disease criteria fulfilled at baseline was 6 (5-8) Resistant to corticosteroids (n=17), DMARDs (n=4), or TNFa inhibitors (n=4) Complete response was defined as the complete resolution of all disease-related symptoms, except for joint erosion	medication included MTX in 13 patients – median dose 12.5 (7.5-20)mg/week, leflunomide at low dose (10mg/day) in one patient and cyclosporine A at 3mg/day in 1 patients. MTX given during follow up in 10 of 13 patients. In 3 patients MTX discontinued 8, 5 and 5 months after remission. In 3 patients MTX added with anakinra later during follow up	**Secondary outcome – safety**	**Frequency of further disease flares -** **Adverse treatment effects –**	improvement of clinical features eg fever, rash, lymphadenopathy, hepatosplenomegaly, [P<0.001], in patients Disease exacerbation in 3 patients (12%). 1 with fever episodes and worsening articular involvement. Second with fever and rash reappearing with deterioration of articular involvement with increase in WBC, ferritin and liver enzymes. 3rd patient in complete remission for 9 months reduced anakinra and presented fever, rash, leucocytosis and elevation of acute-phase reactants 4 months later who went into complete remission within one month after starting anakinra with MTX 15mg/week. 3 patients developed severe urticarial reaction after first months of treatment and discontinued therapy.			only study presenting some results of use of anakinra as adjunct therapy vs. monotherapy showing no significant differences in achievement of complete/partial clinical response or laboratory response as well as no significant difference in adverse events reported [P=1.00]. However it is difficult to establish whether use of a DMARD with anakinra improves its efficacy in all patients. This study does not provide separate results for Group 1 (predominantly with systemic symptoms) and Group2 patients (chronic articular manifestations).

						7 (28%) patients developed infections (one tracheobronchitis, one H1N1 virus infection of URT, one gastroenteritis with fever, one soft tissue abscess, and 3 lower UTI, which led to transient discontinuation of immune-suppressive treatment. 1 patient receiving MTX as concomitant medicine had slight increase in liver enzymes. 5 patients had local hypersensitivity reaction at the site of injection			
				Primary outcome – clinical effectiveness	**Normalisation/improvement of ESR and/or CRP and/or ferritin -**	At 3 months significant reduction in CRP from 111 to 5.4 [P=0.028], ESR from 75 to 11.5 [P=0.04]; and High Ferritin levels(>300ng/ml) reduced in24 (96%) patients to 4 (17%) patients [P=0.004]			
				Primary outcome	**Normalisation/improvement of anaemia and leucocytosis**	Significant reduction in anaemia from 16 (64%) patients (with			

						Hb<12 for males and <13.5 for males) to 5 (21%) patients [P=0.008] with mean Hb increasing from 11.8 to 13.1 [P=0.042] Leucocytosis significant reduction from 21 (84%) patients to 5(21%) [P=0.001]			
				Secondary outcome	**Dosage of prednisolone and DMARDs**	At 1 month significant reduction [P=0.001] in methylprednisolone oral dose from 18mg/d at baseline to 14 at month 1 and 8 at month 3.			
				Primary outcome	**Important to decision-making:** **Physician global assessment of disease activity (PGA)**	At month 3, VAS physician down from 1.8 to 0. [P=0.001] VAS Global down from 2.25 to 0 [P=0.001]			
					Subjective symptom scores –	At month 3 VAS pain down from 2.4 to 0 [P=0.001]			

Use of Anakinra vs. DMARDs to treat Adult-onset Still's disease refractory to MTX, corticosteroids									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
Nordstrom et. al. 2012	An open, Randomized, Multi-centre Study Groups 1 & 2	22 patients in 10 centres in Finland, Norway and Sweden Trial with 2 parallel patient groups with Adult-onset Still's disease refractory to corticosteroids & DMARD Gender = 5F + 5M on DMARD and; 6F + 6M on anakinra Mean age (SD) – DMARD = 39(17) anakinra = 39(18) Median Adult-onset Still's	Open, randomized (1:1) multicentre trial. All patients received – Prednisolone 10mg/day and NSAID if needed. anakinra = 100mg/day with subcutaneous injection in prefilled syringe, or MTX = 10-25mg weekly oral/subcutaneous/intramuscular; AZA = 1-3mg/kg/day oral; LEF = 20mg/day oral; CSA = 2.5-5mg/kg/day divided into 2 oral doses; SSZ 1000-2000 mg/day oral. Two intraarticular	**Primary outcome – clinical effectiveness** **Secondary outcome**	**Response to treatment/Resolution of disease flares/clinical remission e.g. joint manifestations, fever, rash, splenomegaly, lymphadenopathy, hepatomegaly, pericarditis and pleuritis –** **Frequency of further disease flares -**	At week 4, 6/12 with anakinra achieved remission versus 3/10 with DMARD. At week 8, 7/12 with anakinra and 5/10 with DMARD achieved remission. At week 24, 6/12 on anakinra were in remission vs. 2/10 on DMARD. No statistical difference. By week 24 mean prednisolone doses had been reduced in both groups. 3 on anakinra but none on DMARD were able to discontinue oral corticosteroids (p=0.22). 2 pts on DMARD needed 1 intraarticular injection each. During the open label extension (OLE) phase of 28 weeks, majority of patients receiving anakinra completed 52 weeks vs. only 3 patients on DMARD. Half of patients randomised to	6	Applicable	This is an open, randomised, multi-centre study on 22 patients from 10 centres in Finland, Norway and Sweden with refractory AOSD randomised into two groups. The small cohort does not allow statistical testing between groups. Overall, the differences between groups did not reach statistical significance. Precise effects of anakinra on refractory AOSD cannot be determined as it is used in combination with steroids and NSAIDs. This is the only study that offers comparative information of effects from use of anakinra versus DMARDs through randomisation. However, the patient cohort is small and limits the generalisability of findings.

		disease duration in months (range) – DMARD = 19 (3-204) anakinra =14 (2-240) DMARD 12 patient grp (6 MTX, 2 AZA, 2LEF) Fever(1), Rash(8), Swollen joints (2), CRP mean – 25 (0.2-116), Ferritin mean – 186(17-680), Physician's global mean – 21 (2-43), Patients' global mean – 28 (0-65) Prednisolone dose – 18.5 (10-25) anakinra to 12 patients Fever(1), Rash(9), Swollen joints (2), CRP mean – 25 (0.5-104), Ferritin mean –	corticosteroid injections in 24 weeks were allowed. Injection site reactions (ISR) = To alleviate acute pain the syringe was warmed and cold pack applied. Delayed reactions were mitigated by topical hydrocortisone or anti-histamine cream. Randomization was done according to a computer generated blocked list (size of 10). Statistical comparison were made by permutation-type tests. Patients followed up for 24 weeks A 28 week open label extension	**Secondary outcome - safety** **Secondary outcome** **Primary outcome**	**Adverse treatment effects –** **Quality of life -**	DMARD had a disease flare. In OLE they converted to anakinra as monotherapy or combined with DMARD (14 patients) half of whom were in remission at week 52. 3 patients experienced serious adverse effects i.e. worsening of Adult-onset Still's disease (lack of efficacy) – 1 on anakinra and in 2 on DMARD (MTX visit 1 who withdrew; LEF visit 4) 7/12 patients on anakinra reported grade 1 ISR and 1 patient reported grade 2 ISR (Grade III ISR requires hospitalization). Four additional patients reported grade 1 ISR in OLE). No subject withdrew from study More patients on anakinra than DMARD achieved improvements in SF36 physical health summary (p=0.011) Efficacy was assessed			

		354*(18-1740), Physician's global mean – 21 (6-45), Patients' global mean – 25 (3-60), Prednisolone dose – 12.5 (10-60*) *Sig difference	(OLE) with switching or add-on treatment with comparator drug was given if improvement did not occur within 24 weeks Primary end-point was remission – 8 weeks (afebrile in absence of NSAIDS, - decrease of CRP and ferritin & - Normal swollen (SJC) and tender joint counts (TJC)	**– clinical effectiveness** **Secondary outcome** **Secondary outcome**	**Normalisation/improvement of ESR and/or CRP and/or ferritin -** **Dosage of prednisolone and DMARDs** **Subjective symptom scores**	at weeks 8, 12 and 24. Full response was defined as body temp <37 deg C, CRP <10mg/l and ferritin <200 ug/l female, <275ug/l male and normal SJC/TJC, HAQ and SF36. CRP normalised in both groups without any significant difference. By week 24 mean prednisolone doses had been reduced in both groups. 3 on anakinra but none on DMARD were able to discontinue oral corticosteroids (p=0.22). 2 pts on DMARD needed 1 intra-articular injection each. SF36 physical health summary score presented showing more patients on anakinra than on DMARD achieving improvements [P=0.011]			

Use of Tocilizumab to treat Adult-onset Still's disease refractory to MTX, corticosteroids (& Anakinra where stated)									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
Ciprian i P. et.al. 2014	Case series Group 2	11 patients Women-6 Men-5 Mean age – 46.45 (28-73) Mean Adult-onset Still's disease duration – 6.1yrs (1-12) Chronic arthritis -11 (100%) Radiological damage – 7(63%) Fever – 11 (100%) Recurrent systemic flare – 8(72%) NSAIDS and MTX ever used – 11 (100%) MTX ongoing – 8 (72%) Long term corticosteroid therapy – 11 (100%)	Tocilizumab 8mg.kg every 4 weeks for 12 months with 6 months of follow-up after discontinuation – studied in patients not responding to conventional therapies for 3 months or evidence of drug toxicity. 8 patients treated in combination with MTX plus prednisolone 3 patients received tocilizumab plus prednisolon	**Primary outcome – clinical effectiveness**	**Response to treatment/Resolution of disease flares/clinical remission e.g. joint manifestations, fever, rash, splenomegaly, lymphadenopathy, hepatomegaly, pericarditis and pleuritis** **Frequency of further disease flares**	Median disease activity score (DAS28) in 28 joints at baseline- 5.62 Month 3 – 2.31 Month 6 – 1.88 Month 12 – 1.61 EULAR remission (<2.6) achieved in 45.45% (5/11) at 3 months; in 63% (7/11) at 6 months; 81% (9/11) at 12 months. Other achieved EULAR response - <3.2.Statistically significant improvement of joint assessment found after 6 and 12 months of treatment compared to baseline (P<0.05) Remission of fever and systemic symptoms – 11 (100%) 3 patients reported increased number of tender and swollen joint, onset of systemic symptoms	5	Directly applicable but note small cohort size	This case series study presented safety and efficacy data on tocilizumab therapy over 12 months (Jan 2009 to Jan 2012) in AOSD patients refractory to conventional therapy. However, this case series has only 11 patients and tocilizumab is used as both monotherapy and in combination (with MTX or prednisolone or both) and hence exclusive effects of tocilizumab cannot be ascertained. Patients were followed up over 18 months. The average reduction in ESR, CRP, Ferritin and Hb values is not presented but results state reduction and stabilisation of values after month 3 with significant corticosteroid sparing activity and minor adverse events. The study limitation is that it is based on a very small cohort of patients. Data on outcomes related to quality of life, subjective symptom scores and cost effectiveness are unavailable. Results cannot be split to determine the specific effects of tocilizumab on the two AOSD group types.

			e without MTX.			and a worsening of patient VAS global health with high ESR, CRP and ferritin			
				Secondary outcome – safety	**Adverse treatment effects**	Minor adverse events. 1 – URTI 2 – Injection site reactions after one infusion No significant cytopenia			
				Primary outcome – clinical effectiveness	**Normalisation/improvement of ESR and/or CRP and/or ferritin**	ESR, CRP, Ferritin values reduced by month 3 and remained stable by month 12.			
					Normalisation/improvement of anaemia and leucocytosis –	Progressive normalisation of anaemia (Hb) in 7/11 patients with Hb <10 with significant improvement in Hb levels.			
				Secondary outcome	**Dosage of prednisolone and DMARDs**	Prednisolone tapered. Median dose at baseline – 50 (25-100mg/day) Month 3 – 12.5 (12.5-25mg/day) Month 6 – 6.25 (5-12.5mg/day) Month 12 – 0 (0-			

				Primary outcome – clinical effectiveness **Secondary outcome**	**Physician global assessment of disease activity (PGA)** **Subjective symptom scores**	12.5mg/day) After 12 months 8/111 (72%) discontinued corticosteroid therapy Median patient VAS Global Health at Baseline – 75 (80-50)mm 6 months – 35 (0-70)mm 12 months – 0 (0-30)mm Statistically significant improvement (P<0.005) between baseline and each time point – 3, 6, 12 and 18 months At 18 months – 8/11 (72%) patients maintained clinical remission on only MTX			
Ortiz-Sanjuan et.al 2014	Retrospective Multi-centre open-label study	34 patients (8 men, 26 women) mean SD age 38.7 (+/-16.1 years) Diagnosed Adult-onset Still's disease (Yamaguchi	Tocilizumab prescribed as monotherapy (15 cases) or in combination with other synthetic immunosup	**Primary outcome – clinical effectiveness**	**Response to treatment/Resolution of disease flares/clinical remission e.g. joint manifestations, fever, rash, splenomegaly, lymphadenopathy, hepatomegaly, pericarditis and**	After 1 year frequency reductions noted - joint manifest decreased from 97.1% to 32.4% -Cutaneous manifestation and fever from 58.8% to 5.9% -Fever 78% to 22%	7	Directly Applicable but note combination therapies used	This is a multi-centre open label observational retrospective study of 34 refractory Adult-onset Still's disease cases (refractory to synthetic immunosuppressive drugs and biological agents such as Anakinra, Etanercept). tocilizumab is used as monotherapy in 15 cases and as combination treatment in 19 cases. This makes it difficult to ascertain the specific effect of tocilizumab in patients with refractory AOSD. Tocilizumab is administered in varying doses and frequencies. Patients are followed up for 1 year. There is limited scope for

		criteria – Group 2 predominantly . Median Adult-onset Still's disease duration – 4.2years (IQR – 1-9yrs) with inadequate response to corticosteroids and in addition treated with synthetic immunosuppressive drugs with 17 receiving biologic agent with Anakinra 914), Etanercept (7) Joint manifestation (33), fever (20), cutaneous rash (18), lymphadenopathy (10), splenomegaly (2), hepatomegaly (3), pleuritis (1) and pericarditis(2)	pressive (19) MTX(91%) Initial dose I.V. 8mg/kg every 4 weeks (22 cases), 8mg/kg every 2 weeks (10 cases), 4mg/kg every 4 weeks (2 cases) Maintenance dose of tocilizumab was4-8mg/kg every 2 weeks or every 4 weeks	**Secondary outcome – safety**	**pleuritis** **Frequency of further disease flares** **Adverse treatment effects**	-Incidence of Lymphadenopathy from 29.4% to 0% Rapid improvement in systemic symptoms such as fever and cutaneous manifestations observed but joint manifestations were refractory to Rx with 32.4% patients had persistent joint involvement after 1 year of tocilizumab therapy. After median follow up of 19 months infections were most common complications. 2 discontinued due to severe infection (1 pyelonephritis and acute enterocolitis and 1 bacterial spondylodiscitis. Other infections incl. pneumonia (1), URTI(3), dental infection (1), urinary infection (1), EpsteinBarr (1), herpes zoster (1). Mild leukopenia (4), elevated hepatic enzyme levels(4),			generalisability due to the lack of a comparator and the small cohort size and the results available do not address all the outcomes listed in the PICO. Overall the results suggest that there may be a differential effect on joint manifestations compared to systemic manifestation but this is based on a small number of patients (n=34)

		Anaemia (15), leucocytosis (19), a high CRP (28), increased ESR (27)		**Primary outcome – clinical effectiveness**	**Normalisation/improvement of ESR and/or CRP and/or ferritin –**	hypercholesterolemia (1), headache (1). Frequency of abnormal elevation of CRP down – 82.4.2% to 23.5%; ESR down – 79.4% to 2.9% - High serum ferritin levels from 47.1% to 2.9% of pts.			
				Primary outcome – clinical effectiveness	**Normalisation/improvement of anaemia and leucocytosis** –	Leucocytosis decreased from – 55.9% to 17.6% Anaemia from 44.1% to 2.9%			
				Secondary outcome	**Dosage of prednisolone and DMARDs**	Significant corticosteroid sparing effect (P=<0.05) from median Prednisolone 13.8mg/day at baseline to 2.5mg at year			

Puechal et.al. 2011	Prospective cohort study	14 patients aged 18+ with intractable refractory Adult-onset Still's disease who fulfilled the Yamaguchi criteria with Group 2 predominantly and treated with off-label tocilizumab in France between July 2006 and July 2009 were included by obtaining information from French Agency for Safety of Health Products. All patients had experienced failure or intolerance with MTX and Anakinra and 12 with at least one anti-TNF Females – 9; Males – 5 Mean age –	Data on 14 patients all patients receiving at least 1 infusion of tocilizumab were evaluated. Results analysed at baseline, at 3 & 6 months. In 9 patients tocilizumab 8mg/ kg every 4 weeks In 4 patients tocilizumab started at 8mg/kg every 2 weeks, 1 of whom was given injections at 3 week intervals. 1 patient – 5mg/kg infusion monthly. Combinations - 8 = MTX 2 = LEF 4 =	**Primary outcome – clinical effectiveness**	**Response to treatment/Resolution of disease flares/clinical remission e.g. joint manifestations, fever, rash, splenomegaly, lymphadenopathy, hepatomegaly, pericarditis and pleuritis** **Frequency of further**	Clinical improvement in arthritis activity evaluated using the European League Against Rheumatism (EULAR) criteria. Improvement in systemic features was defined as the resolution of systemic symptoms 11 patients successfully completed the 6 month study Resolution of systemic symptoms (fever & eruption) was observed for 86% patients (6/7) at 3 and 6 months. Mean DAS28 dropped from 5.61 to 3.21 at month 3 and to 2.91 at month 6. Good EULAR response achieved in 64% patients (9/14) at 3 and 6 months. EULAR remission was achieved in 36% of patients (5/14) at 3 months and 57% (8/14) at 6 months 2 patients withdrew due to side-effects	5	Directly applicable but note combination therapies used	This prospective cohort study of 14 patients is an observational uncontrolled study. Tocilizumab has been used in varying doses and in combination with MTX(8), LEF(2) and as monotherapy and results are pooled for the entire cohort making it difficult to ascertain the specific efficacy of Tocilizumab as a monotherapy in steroid and MTX refractory AOSD. The history of medications used previously included Anakinra however it is difficult to establish if tocilizumab treatment was superior to Anakinra as no previous history is available and this is not a head to head comparison. As it is a retrospective study previous drug history is limited to the data that is available and not all the results on the outcomes listed in the PICO are available. There is no comparator group and no randomisation and owing to the small cohort size so scope for generalisability of findings is limited.

		38.4 (23-68) Adult-onset-9 Child onset-5 Disease duration (yrs) mean – 13.6 (3-27) Chronic Arthritis – 8 H/o of recurrent systemic flares – 11 MTX every used (14); ongoing (8) Anakinra ever used – 14 Anti-TNF drugs ever used – 12 Abtacept, rituximab, or IVIG ever used – 7 Long term corticosteroids treatment – 14 Irreversible joint damage in 8 patients Out of 28 joint-count, mean tender joints were 10.5, mean swollen joints were 7.9 and mean DAS28 was 5.61 At baseline in	tocilizumab monotherapy All patients – Prednisolone mean dose – 23.3mg/day Median dose15.5 (5 - 80)	**Secondary outcome – safety**	**disease flares** **Adverse treatment effects**	and a 3rd due to systemic flare. A 56 year old female with high BP and DM with 9yr h/o Adult-onset Still's disease treated with anti-TNFs developed necrotizing angiodermatitis leading to discontinuation. Cutaneous outcome was favourable despite arthritis flare after tocilizumab withdrawal. A 30 year female experienced chest pain and chills after each tocilizumab infusion leading to discontinuation of treatment at month 3 A 68 year old patient had increased arthralgia and CRP values after tocilizumab was initiated so treatment was stopped. Mild hyperlipidaemia was observed in one patient and increased alanine aminotransferase levels in another patient. No infection was observed.			

		addition to arthritis, recurrent systemic involvement incl fever and rash was present in 7 patients. Median ESR – 36.5mm/hr (2-120) Median CRP – 5.2(0.3-27.2). Serum ferritin – 1,939 +/- 4,685		**Primary Outcome – clinical effectiveness** **Primary Outcome – clinical effectiveness** **Secondary outcome-**	**Normalisation/improvement of ESR and/or CRP and/or ferritin –** **Normalisation/improvement of anaemia and leucocytosis** – **Dosage of prednisolone and DMARDs**	The median ESR dropped from 36.5 (2-120) mm/hr at baseline to 8.0(1-98) at month 3 and 12.5 (1-91) at month 6 Serum ferritin level dropped from median1939ng/ml to 132 at month 3 and 209 at month 6. CRP reduced from baseline median value of 5.2 to 0.5 at month 3 and 0.6 at month 6 Leukocyte count dropped from median 10.65 (+/-5.56) to 9.8 (+/-6.0) at month 3 and to 9.03 (+/-3.01) at month 6 Prednisolone dosage was reduced to a mean of 13mg/day (median, 13.5, range 0-25) at 3 months and to mean 10.3mg/day (median, 11, range 0-20) at 6 months 7 patients had a corticosteroid dosage of 10mg/day or less at 6 months. No co-relation was found between the			

					Adherence to treatment	tocilizumab dose and achievement of arthritis or systemic remission or with the decrease of corticosteroids. At month 6 there was a 60% improvement in number of tender joints, swollen joints and mean visual assessment score for patient global health.			
Elkayam et. al. (2014)	Questionnaire based retrospective survey of Israelis rheumatologists who had ever treated patients with AOSD	15 AOSD patients 9 Male 6 Female Mean age – 33 (+/-12) Mean disease duration – 9 (+/- 11) Arthralgia – 15 (100%) Fever–9(60%) Rash–7(46%) Pleuritis-3(20%) Mean prednisolone dose – 27.6mg/d (+/-26.3) DMARD mean – 3.6 (1-7) Previous treatment with	12 patients received Intravenous tocilizumab 8mg/kg/month 3 received 8mg/kg twice a month	**Primary outcome – clinical effectiveness**	**Response to treatment/Resolution of disease flares/clinical remission e.g. joint manifestations, fever, rash, splenomegaly, lymphadenopathy, hepatomegaly, pericarditis and pleuritis** **Adverse treatment effects**	After 6 months, significant reduction in mean tender joints from 11.6 to 2, and mean swollen joints from 8.6 to 1.09. (P<0.05) Resolution of systemic symptoms in 86% patients with no fever in patients reported after 6 months of treatment Good EULAR response reported in 64% of 14 patients at 3 months and EULAR remission in 57% of those patients after 6 months 1 patient developed MAS after 11	5	Directly applicable but note limitations and small cohort size	This study is a retrospective survey based study with a small sample relying on results provided by the treating rheumatologists surveyed which may limit the generalisability of findings. The study mentions that patients are refractory to corticosteroids and DMARD but does not mention if methotrexate is specifically used as a DMARD. Tocilizumab is administered with a corticosteroid and effects of tocilizumab in different types of AOSD cannot be ascertained from pooled results. Adverse events may be under-reported as this was a retrospective survey.

		1 or >1 TNF – 10 (66%) Mean tender joints – 11.6 (+/-6.8) Mean swollen joints – 8.6 (+/- 5.4)				months, unclear if due to tocilizumab – switched to Canakinumab with complete resolution of symptoms and normalisation of acute phase response			
				Secondary outcome – safety	**Normalisation/improvement of laboratory measures of disease activity to inform on risk of amyloidosis (serum amyloid A protein level (SAA))**	1 patient had amyloidosis secondary to longstanding Still's disease and after treatment with tocilizumab normalisation of acute-phase response, accompanied by resolution of proteinuria, occurred, suggesting a regression of amyloidosis			
				Primary outcome – clinical efficacy	**Normalisation/improvement of ESR and/or CRP and/or ferritin –**	Significant reduction in mean ESR at 6 months reduced from 60mm/h (+/-28) to 3.9 (+/-1.4) (P<0.05) and CRP reduced from – 11.6 (+/-15) to 0.5 (+/-0.5) (P<0.05)			
				Secondary Outcome	**Dosage of prednisolone and DMARDs**	Significant reduction in mean prednisolone dose from 27.6mg/d (+/-			

						26.3) to 4.9mg/d (+/- 4) (P<0.05)			

7. Grade of evidence table

Anakinra

Outcome Measure	Reference	Quality of Evidence Score)	Applicability	Grade of Evidence	Interpretation of Evidence
Response to treatment/Resolution of disease flares/clinical remission e.g. joint manifestations, fever, rash, splenomegaly, lymphadenopathy, hepatomegaly, pericarditis and pleuritis	Ortiz-Sanjuan, 2015	7	Directly applicable but note small numbers	B	In the study by Ortiz-Sanjuan (2015), cutaneous manifestations decreased from 58.5% to 7.3%; Fever decreased from 78% to 22%. Lymphadenopathy decreased from 26.8% to 4.9% At 1 year joint involvement was 41.5%. The study design means there is a lack of information on potential confounding factors. As anakinra was prescribed in combination with other drugs and pooled results are presented it is not possible to ascertain its efficacy as a monotherapy. Long term efficacy cannot be determined due to limited follow up. Limited statistical testing.
	Nordstrom, 2012	6	Directly applicable as comparative study		
	Giampetro, 2013	6	Directly applicable but note small numbers and limitations		
	Lequerre T et.al. 2008	5	Applicable but contains small number of patients and limitations		
	Laskari et.al. 2011	6	Applicable but has limitations and a small cohort		

Frequency of further disease flares	Giampetro, 2013	6	Directly applicable but note small numbers and limitations	B	In the study by Giampetro et al (2013) 15 patients went into remission at 3 months. This retrospective questionnaire based study is likely to be limited due confounding bias. The results are not tested for statistical significance and apply to a small cohort of patients with limited follow up. The specific impact on the two types of AOSD cannot be determined as results are pooled. Patients received the drug as monotherapy and in combination.
	Laskari et.al. 2011	6	Applicable but has limitations and a small cohort		
Adverse treatment effects	Ortiz-Sanjuan, 2015	7	Direct applicable but note small numbers	B	In the study by Ortiz-Sanjuan et.al (2015), (n=41) after a median follow up of 16 months, cutaneous reactions were the most common complication with 2 out of 8 patients discontinuing treatment. In 2 patients treatment had to be discontinued due to severe infections. Other adverse treatment effects reported were leukopenia and myopathy. It is not possible to determine the specific effects of anakinra as monotherapy since it was prescribed in combination with other drugs.
	Nordstrom, 2012	6	Directly applicable but as comparative study		
	Giampetro, 2013	6	Directly applicable but note small numbers and limitations		
	Lequerre T et.al. 2008	6	Applicable but contains small number or patients and limitations		
	Laskari et.al. 2011	6	Applicable but has limitations and a small cohort		

Quality of life	Nordstrom, 2012	6	Directly applicable but as comparative study	C	Nordstrom et. al. 2012 used the SF-36 physical health summary and report that more patients on anakinra than DMARD achieved improvement. This is an open, randomised, multi-centre study but the small cohort does not allow statistical testing between groups and limits generalisability. Precise effects of anakinra on refractory AOSD cannot be determined as it is used in combination with steroids and NSAIDs.
Normalisation/improvement of ESR and/or CRP and/or ferritin	Ortiz-Sanjuan, 2015	7	Direct applicable but note small numbers	B	Erythrocyte sedimentation rate, C- Ortiz-Sanjuan et.al (2015) reported the prevalence of abnormal elevation of CRP reduced from 90.2% to 46.3%, high ESR reduced from 78% to 22% and high serum ferritin levels reduced from 63.4% to 36.6% in the patient cohort. The study design means there is a lack of information on potential confounding factors. As anakinra was prescribed in combination with other drugs and pooled results are presented it is not possible to ascertain its efficacy as a monotherapy. Long term efficacy cannot be determined due to limited follow up. Limited statistical testing. .

	Nordstrom, 2012	6	Directly applicable but as comparative study		
	Giampetro, 2013	6	Directly applicable but note small numbers and limitations		
	Lequerre T et.al. 2008	5	Applicable but contains small number or patients and limitations		
	Laskari et.al. 2011	6	Applicable but has limitations and a small cohort		
Normalisation/improvement of anaemia and leucocytosis	Ortiz-Sanjuan, 2015	7	Direct applicable but note small numbers	B	Anaemia (specifically iron deficiency), hyperferritinaemia and leucocytosis are commonly observed in adult-onset Still's disease. Ortiz-Sanjuan et.al (2015), reported a reduction in anaemia from 56.1% to 9.8% and leucocytosis from 65.9% to 14.6%. No statistical testing was undertaken to quantify these changes, anakinra was prescribed with other medications and the study design means that confounding factors were not controlled for.
	Nordstrom, 2012	6	Directly applicable but as comparative study		
	Giampetro, 2013	6	Directly applicable but note small numbers and limitations		
	Lequerre T et.al. 2008	5	Applicable but contains small number or patients and limitations		
	Laskari et.al. 2011	6	Applicable but has limitations and a small		

			cohort		
Dosage of prednisolone and DMARDs	Ortiz-Sanjuan, 2015	7	Direct applicable but note small numbers	B	Prolonged use of corticosteroids especially in high doses can cause severe side effects. Ortiz Sanjuan et.al (2015) reported significant prednisolone sparing effects (P=<0.05) reduced from median 20mg/day at baseline to 5mg at 1 year. Anakinra was administered with other drugs so it is not possible to isolate its specific effect. The study design many not have taken into account all confounding factors and results were pooled for both sub-types of AOSD so it was not possible to determine whether this effect was more pronounced in one group. .
	Nordstrom, 2012	6	Directly applicable but as comparative study		
	Giampetro, 2013	6	Directly applicable but note small numbers and limitations		
	Lequerre T et.al. 2008	5	Applicable but contains small number or patients and limitations		
	Laskari et.al. 2011	6	Applicable but has limitations and a small cohort		
Physician global assessment of disease activity (PGA)	Lequerre T et.al. 2008	5	Applicable but contains small number or patients and limitations	B	Laskari et al (2011) reported at month 3, VAS physician score was down from 1.8 to 0. [P=0.001] and the VAS Global score was down from 2.25 to 0 [P=0.001]. The retrospective case series design has a very small cohort of

					patients not all of whom met the Yamaguchi criteria and the patient characteristics presented make it difficult to determine if all patients were refractory to steroids and MTX. As data was collected retrospectively there may have been incompleteness in the data. .
	Laskari et.al. 2011	6	Applicable but has limitations and a small cohort		
Subjective symptom scores	Nordstrom et.al, 2012	6	Directly applicable but as comparative study	B	SF-36 is a generic, validated quality of life measure. Nordstrom et.al (2012) reported using the SF36 physical health summary score which showed more patients on anakinra than on DMARD achieving improvements (P=0.011). This is an open, randomised, multi-centre study which had a very small cohort of patients limited generalisability. There may be reporting bias due to the study design. Anakinra was taken in combination with steroids and NSAIDs so it is challenging to determine its specific effects.
	Laskari et.al. 2011	6	Applicable but has limitations and a small cohort		
Adherence to treatment	Ortiz-Sanjuan, 2015	7	Direct applicable but note small numbers	B	Ortiz-Sanjuan et.al (2015) [n=41], reported that after 1 year 14 patients (34%) discontinued anakinra. Patients were on other treatments alongside anakinra so the lack of adherence cannot be
	Nordstrom, 2012	6	Directly applicable but as comparative study		

					specifically attributed to that single drug.
	Giampetro, 2013	6	Directly applicable but note small numbers and limitations		
	Laskari et.al. 2011	6	Applicable but has limitations and a small cohort		

Tocilizumab

Outcome Measure	Reference	Quality of Evidence Score)	Applicability	Grade of Evidence	Interpretation of Evidence
Response to treatment/Resolution of disease flares/clinical remission e.g. joint manifestations, fever, rash, splenomegaly, lymphadenopathy, hepatomegaly, pericarditis and pleuritis	Cipriani et. al. (2014)	5	Applicable but note small numbers	B	A response to treatment can be measured as resolution of disease flares and clinical remission. Ortiz-Sanjuan et.al (2014), reported at 1 year that cutaneous manifestations and fever reduced from 58.8% to 5.9%, lymphadenopathy from 29.4% to 0% but joint manifestations were refractory to treatment compared to systemic manifestations with 32.4% patients having persistent joint involvement after 1 year of therapy This is a multi-centre open label observational retrospective study with a small cohort of patients some of whom received tocilizumab as monotherapy and some in combination. This aspect of the study design makes it difficult to ascertain the specific effect of tocilizumab There is also limited scope for generalisability due to the lack of a comparator.
	Ortiz-Sanjuan et. al. (2014)	7	Directly applicable but combination therapies used		
	Puechal et. al. (2011)	5	Directly applicable but combination therapies used		
	Elkayam et.al. (2014)	5	Applicable but has limitations and small cohort of patients		
Frequency of further disease flares	Cipriani et. al. (2014)	5	Applicable but note small numbers	B	Cipriani et. al. (2014) reported 3 patients with increased numbers of tender and swollen joints, onset of systemic symptoms and a worsening of patient VAS global health score with high ESR, CRP and ferritin.
	Puechal et. al. (2011)	5	Directly applicable but combination therapies used		

					This case series study included only 11 patients limiting its generalisability and used tocilizumab in both mono- and combination therapy making specific effects difficult to ascertain. Data on outcomes related to quality of life, subjective symptom scores and cost effectiveness are unavailable. Results cannot be split to determine the specific effects of tocilizumab on the two AOSD group types
Adverse treatment effects	Cipriani et. al. (2014)	5	Applicable but note small numbers	B	Adverse effects of the treatment ranges from localised rashes at injection site to systemic or articular disease flares to severe infections which can even lead to discontinuation of treatment. Ortiz-Sanjuan et.al (2014) reported that infections were common at 19 months follow up. This multi-centre open label observational retrospective study reported on a small patient cohort with tocilizumab used as both monotherapy and in combination. This makes it difficult to ascertain the specific effect of the drug. There was no comparator group in the study.
	Ortiz-Sanjuan et. al. (2014)	7	Directly applicable but combination therapies used		
	Puechal et. al. (2011)	5	Directly applicable but combination therapies used		
	Elkayam et.al. (2014)	5	Applicable but has limitations and small cohort of patients		
Normalisation/improvement	Cipriani et. al.	5	Applicable but note small	B	Erythrocyte sedimentation rate, C-

of ESR and/or CRP and/or ferritin	(2014)		numbers		reactive protein and serum ferritin are important biological markers. Ortiz-Sanjuan et.al (2014) reported reduction of ESR from 79.4% to 2.9%, reduction of CRP from 82.4% to 23% and high serum ferritin levels reduced from 47.1% to 2.9%. This is a multi-centre open label observational retrospective study reported on a small number of patients. There is limited scope for generalisability due to the lack of a comparator and the small cohort size and the results available do not address all the outcomes listed in the PICO.
	Ortiz-Sanjuan et. al. (2014)	7	Directly applicable but combination therapies used		
	Puechal et. al. (2011)	5	Directly applicable but combination therapies used		
	Elkayam et.al. (2014)	5	Applicable but has limitations and small cohort of patients		
Normalisation/improvement of anaemia and leucocytosis	Cipriani et. al. (2014)	5	Applicable but note small numbers	B	Anaemia, hyperferritinaemia and leucocytosis are commonly observed in adult-onset Still's disease. Ortiz-Sanjuan et.al (2014) reported leucocytosis decreased from 55.9% to 17.6% and anaemia from 44.1% to 2.9%. This multi-centre open label observational retrospective study reported on a small number of patients on tocilizumab as monotherapy and in combination. The nature of the study leaves considerable scope for bias in reporting outcomes.
	Ortiz-Sanjuan et. al. (2014)	7	Directly applicable but combination therapies used		
	Puechal et. al. (2011)	5	Directly applicable but combination therapies used		

Dosage of prednisolone and DMARDs	Cipriani et. al. (2014)	5	Applicable but note small numbers	B	Prolonged use of corticosteroids especially in high doses can cause several unwanted side effects. Cipriani et.al (2014) reported prednisolone was tapered from the baseline median dose of 50mg/day to 12.5mg/day at month 3 and after 12 months 8/11 patients discontinued corticosteroid therapy. However this case series refers to a very small number of patients with the drug used as both monotherapy and in combination. Case series do not take account of confounding factors and in the study tocilizumab is used as both monotherapy and in combination.
	Ortiz-Sanjuan et. al. (2014)	7	Directly applicable but combination therapies used		
	Puechal et. al. (2011)	5	Directly applicable but combination therapies used		
	Elkayam et.al. (2014)	5	Applicable but has limitations and small cohort of patients		
Physician global assessment of disease activity (PGA)	Cipriani et. al. (2014)	5	Applicable but note small numbers	C	PGA is a recognised tool to monitor health improvement and measure and track patient outcomes. Cipriani et.al (2014) reported median patient VAS baseline of 75 reducing to 35 at month 6 and 0 at 1 year post therapy with statistically significant improvement (P<0.005). This case series reported on a very small number of patients with the drug being used as both monotherapy and in combination.

Subjective symptom scores	Puechal et. al. (2011)	5	Directly applicable but combination therapies used	C	The SF-36 is a validated tool to measure patient's quality of life. Puechal et.al (2011) reported 60% improvement in the number of tender joints, swollen joints and mean visual assessment score for patients' global health. This prospective cohort study included a very small number of patients and there was no control group and no randomisation. Tocilizumab was used as both single therapy and in combination and at differing doses making it challenging to ascertain the distinct effect of the drug and the optimal dose/frequency. .
Adherence to treatment	Cipriani et. al. (2014)	5	Applicable but note small numbers	C	Cipriani et.al (2014) reported all 11 patients successfully completed treatment with tocilizumab. 72% patients (8/11) maintained clinical remission on only methotrexate. However this is an extremely small case series and therefore has limited generalisability.

8. Factsheet

Intervention Fact Sheet	
What is the intervention for?	Adult onset Stills disease
Who might consider taking it?	Patients with Adult-onset Still's disease who have shown partial or incomplete remission of their disease after taking corticosteroids and methotrexate
Who should not take it?	Patients who are pregnant, those who have significant infections or risk of infection should not take these therapies.
Other things to consider	Published studies showing clinical effectiveness and safety of these interventions are based on small cohorts of patients and few of the results obtained are statistically significant. Clinical efficacy of anakinra and tocilizumab as monotherapy in refractory adult-onset Still's disease could not be determined exclusively as both drugs were used in combination with other drugs in majority of patients. It was not possible to determine which sub-group could most benefit from the use of the drug.
Benefits of the intervention	Both anakinra and tocilizumab have shown potential clinical effectiveness in patients with adult-onset Still's disease by improving systemic features such as fever, skin rash, enlargement of organs such as spleen or liver, as well as haematological and serological markers (assessed through blood tests) which are caused by inflammation. Improvement in the articular features - such as joint pain and/or swelling - has been less significant compared to the improvement in systemic signs and symptoms. Studies have reported variable evidence on the impact of the drugs on outcomes such as disease activity scores or EULAR remission, subjective symptom scores and Physician's global assessment tools – which are recognised measures of disease activity. Some studies also demonstrated that patients required lower doses of steroids sparing after introduction of these drugs. However this was often in combination with other drugs.

Harms of the intervention	Adverse events associated with use of anakinra included localised skin reactions (ranging from mild to severe) at the injection site and infections. In some patients this has led to discontinuation of treatment. Other side effects include liver function abnormalities, reduced numbers of white blood cells and increased disease activity (systemic or arthritic flares). Adverse events associated with Tocilizumab include infections, low white blood cells, liver inflammation and systemic or arthritic flare. Injection site reactions are also common and can be severe.

9. Literature search terms

Search strategy *Indicate all terms to be used in the search*	
P – Patients / Population Which patients or populations of patients are we interested in? How can they be best described? Are there subgroups that need to be considered?	Adults with confirmed systemic Adult-onset Still's disease (Group 1) (based on clinical criteria, for example Yamagushi) whose symptoms and biochemical markers remain inadequately controlled after treatment with MTX and corticosteroids or are unable to take these treatments due to side effects Adults with confirmed systemic Adult-onset Still's disease (Group 1) (based on clinical criteria, for example Yamagushi) whose symptoms and biochemical markers remain inadequately controlled after treatment with MTX and corticosteroids and Anakinra Adults with confirmed systemic Adult-onset Still's disease (Group 2) (based on clinical criteria, for example Yamagushi) whose symptoms and biochemical markers remain inadequately controlled after treatment with MTX and corticosteroids
I – Intervention Which intervention, treatment or approach should be used?	Anakinra *Tocilizumab*
C – Comparison What is/are the main alternative/s to compare with the intervention being considered?	Best supportive care – methotrexate and/or corticosteroids and/or other DMARDs Canakinumab for group 1 Etanercept (anti-TNF) for group 2 (*chronic arthritis predominant form only patients)*
O – Outcomes What is really important for the patient? Which outcomes should be considered? Examples include intermediate or short-term outcomes; mortality; morbidity and quality of life; treatment complications; adverse effects; rates of relapse; late morbidity and re-admission	*Critical to decision-making:* Response to treatment/Resolution of disease flares/clinical remission e.g. joint manifestations, fever, rash, splenomegaly, lymphadenopathy, hepatomegaly, pericarditis and pleuritis Frequency of further disease flares Adverse treatment effects

	Quality of life Normalisation/improvement of laboratory measures of disease activity to inform on risk of amyloidosis (serum amyloid A protein level (SAA)) Normalisation/improvement of ESR and/or CRP and/or ferritin Normalisation/improvement of anaemia and leucocytosis Dosage of prednisolone and DMARDs *Important to decision-making:* Physician global assessment of disease activity (PGA) Subjective symptom scores Adherence to treatment Cost effectiveness
Assumptions / limits applied to search	
Inclusion Criteria	English language 1990 to present Randomised studies, non-randomised prospective cohort studies, case-control studies, case series, n of 1 studies.
Exclusion Criteria	Studies older than 1990

Criteria used to include or exclude published studies identified through the search of evidence databases:

Inclusion criteria – Study or research should provide information related to the following on its own or in combination –

a. Clinical effectiveness of anakinra in refractory adult-onset Still's disease – group 1
b. Cost effectiveness of anakinra in refractory adult-onset Still's disease – group 1
c. Clinical effectiveness of tocilizumab in treatment of adult-onset Still's disease – groups 1 & 2
d. Cost effectiveness of tocilizumab in comparison to comparative therapies
e. Comparative clinical and cost effectiveness of anakinra in Group 1
f. Comparative clinical and cost effectiveness of tocilizumab in Group 1 & 2

2. Randomised studies, non-randomised prospective cohort studies, case-control studies, case series, are included, as stated in the PICO. In addition, retrospective studies which provide information on clinical effectiveness of interventions are also included.

Exclusion criteria –

1. Studies that do not meet the inclusion criteria based on the research questions stated in the PICO have been excluded.
2. Research papers not published in recognised journals or guidelines with insufficient information to address the research questions have been excluded
3. Poster presentations, abstracts only papers, letters to editors, papers where payment was required and pre-publication papers were excluded with the exception of publications that provided evidence around safety of the interventions under review which have been referenced.

Papers that were not published in recognised national and international journals and case reports that do not meet the full inclusion criteria have been excluded.

10. Search strategy

Search strategy *Indicate all terms used in the search*

***Group 1* – NICE Evidence, Cochrane Library, TRIP Database Pro:**

("adult Still's disease" OR "adult-onset Still's disease" OR "adult onset Still's disease" OR "adult Stills disease" OR "adult-onset Stills disease" OR "adult onset Stills disease" OR Adult-onset Still's disease) AND (Anakinra OR Kineret OR canakinumab)

Medline:

1. Medline; ("adult Still's disease" OR "adult-onset Still's disease" OR "adult onset Still's disease" OR "adult Stills disease" OR "adult-onset Stills disease" OR "adult onset Stills disease" OR Adult-onset Still's disease).ti,ab; 1135 results.

2. Medline; exp STILL'S DISEASE, ADULT-ONSET/; 1055 results.

3. Medline; (Anakinra OR Kineret OR canakinumab).ti,ab; 1243 results.

4. Medline; 1 OR 2; 1376 results.

5. Medline; 3 AND 4; 80 results.

6. Medline; 5 [Limit to: Publication Year 1990-2016 and (Language English)]; 71 results.

Embase:

7. EMBASE; ("adult Still's disease" OR "adult-onset Still's disease" OR "adult onset Still's disease" OR "adult Stills disease" OR "adult-onset Stills disease" OR "adult onset Stills disease" OR Adult-onset Still's disease).ti,ab; 1588 results.

8. EMBASE; exp ADULT ONSET STILL DISEASE/; 1385 results.

9. EMBASE; (Anakinra OR Kineret OR canakinumab).ti,ab; 2603 results.

10. EMBASE; 7 OR 8; 1966 results.

11. EMBASE; 9 AND 10; 161 results.

12. EMBASE; 11 [Limit to: English Language and Publication Year 1990-2016]; 149 results.

CINAHL:

13. CINAHL; ("adult Still's disease" OR "adult-onset Still's disease" OR "adult onset Still's disease" OR "adult Stills disease" OR "adult-onset Stills disease" OR "adult onset Stills disease" OR Adult-onset Still's disease).ti,ab; 81 results.

14. CINAHL; exp STILL'S DISEASE, ADULT-ONSET/; 97 results.

15. CINAHL; (Anakinra OR Kineret OR canakinumab).ti,ab; 184 results.

16. CINAHL; 13 OR 14; 120 results.

17. CINAHL; 15 AND 16; 10 results.

18. CINAHL; 17 [Limit to: Publication Year 1990-2016 and (Language English)]; 10 results.

Group 2 – **NICE Evidence, Cochrane Library, TRIP Database Pro:**

("adult Still's disease" OR "adult-onset Still's disease" OR "adult onset Still's disease" OR "adult Stills disease" OR "adult-onset Stills disease" OR "adult onset Stills disease" OR Adult-onset Still's disease) AND (Tocilizumab OR Actemra OR RoActemra OR atlizumab OR etanercept OR Enbrel OR "anti-TNF" OR "TNF inhibit*" OR "TNF block*")

Medline:

1. Medline; ("adult Still's disease" OR "adult-onset Still's disease" OR "adult onset Still's disease" OR "adult Stills disease" OR "adult-onset Stills disease" OR "adult onset Stills disease" OR Adult-onset Still's disease).ti,ab; 1135 results.

2. Medline; exp STILL'S DISEASE, ADULT-ONSET/; 1055 results.

3. Medline; (Tocilizumab OR Actemra OR RoActemra OR atlizumab OR etanercept OR Enbrel OR "anti-TNF" OR "TNF inhibit*" OR "TNF block*").ti,ab; 14129 results.

4. Medline; 1 OR 2; 1376 results.

5. Medline; 3 AND 4; 104 results.

6. Medline; 5 [Limit to: Publication Year 1990-2016 and (Language English)]; 83 results.

Embase:

7. EMBASE; ("adult Still's disease" OR "adult-onset Still's disease" OR "adult onset Still's disease" OR "adult Stills disease" OR "adult-onset Stills disease" OR "adult onset Stills disease" OR Adult-onset Still's disease).ti,ab; 1590 results.

8. EMBASE; exp ADULT ONSET STILL DISEASE/; 1386 results.

9. EMBASE; (Tocilizumab OR Actemra OR RoActemra OR atlizumab OR etanercept OR Enbrel OR "anti-TNF" OR "TNF inhibit*" OR "TNF block*").ti,ab; 27839 results.

10. EMBASE; 7 OR 8; 1968 results.

11. EMBASE; 9 AND 10; 194 results.

12. EMBASE; 11 [Limit to: English Language and Publication Year 1990-2016]; 169 results.

CINAHL:

13. CINAHL; ("adult Still's disease" OR "adult-onset Still's disease" OR "adult onset Still's disease" OR "adult Stills disease" OR "adult-onset Stills disease" OR "adult onset Stills disease" OR Adult-onset Still's disease).ti,ab; 81 results.

14. CINAHL; exp STILL'S DISEASE, ADULT-ONSET/; 97 results.

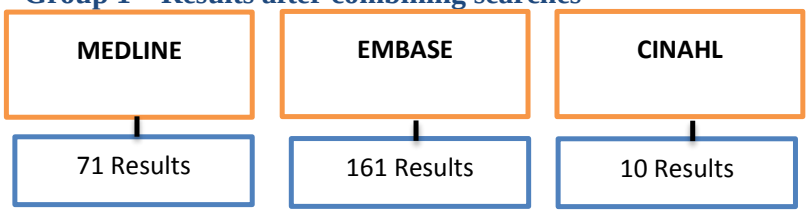
15. CINAHL; 13 OR 14; 120 results.

16. CINAHL; (Tocilizumab OR Actemra OR RoActemra OR atlizumab OR etanercept OR Enbrel OR "anti-TNF" OR "TNF inhibit*" OR "TNF block*").ti,ab; 1512 results.

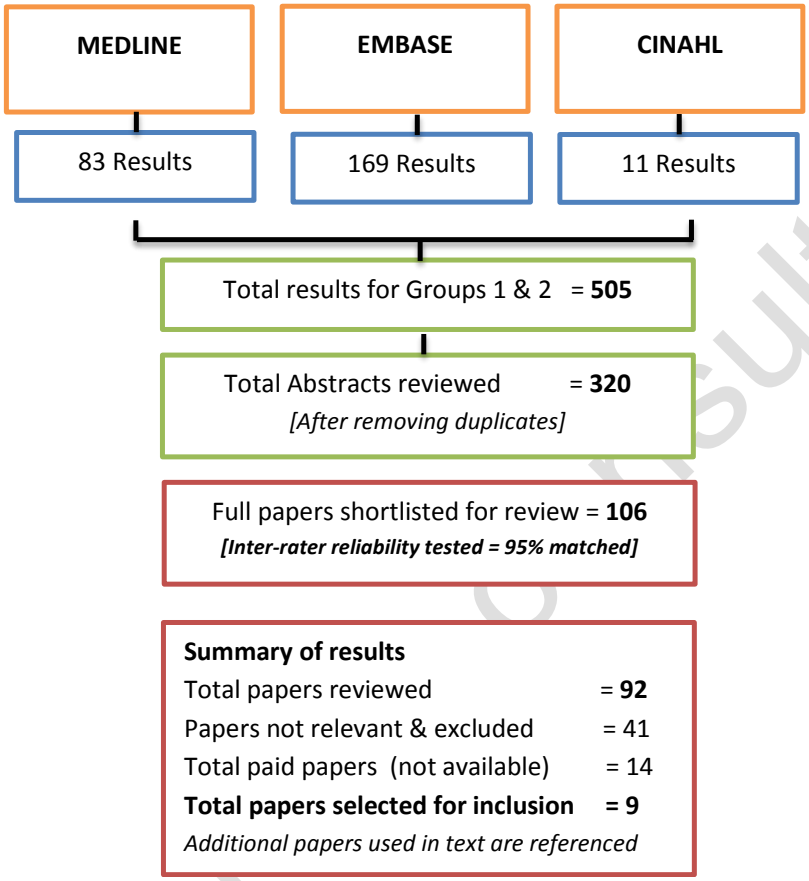
17. CINAHL; 15 AND 16; 11 results.

18. CINAHL; 17 [Limit to: Publication Year 1990-2016 and (Language English)]; 11 results.

Group 1 – Results after combining searches



Group 2 – Results after combining searches



11. Evidence selection

- Total number of publications reviewed: 106
- Total number of publications considered relevant: 32
- Total number of publications selected for inclusion in this review: 9

Eleven additional publications reviewed to gain more information on safety and adverse events are referenced.

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Abbreviations

ADA	Adalimumab
AOSD	Adult-Onset Still's Disease
ANA / ANK	Anakinra
AZA	Azathioprine
CAPS	Cryopyrin Associated Periodic Syndrome
CPM	Cyclophosphamide
CRG	Clinical Reference Group
CsA	Cyclosporine A
DAS	Disease Activity Score
DMARD	Disease Modifying Anti-Rheumatic Drugs
EMA	European Medicines Agency
ETN	Etanercept
ESR	Erythrocyte Sedimentation Rate
EULAR	European League Against Rheumatism
GRADE	Grading of Recommendations Assessment, Development and Evaluation
H	Hours
HAQ	Health Assessment Questionnaire
HB	Haemoglobin
HCQ	Hydroxychloroquine
IFX	Infliximab
IL	Interleukin
IQR	Inter-Quartlie Range
ISR	Injection Site Reaction
IVIg	Intra-Venous Immuno-globulin
/mg	Per milligram
LFN	Leflunomide
LFT	Liver Function Tests
MAS	Macrophage Activation Syndrome
Mg/l	Milligram per litre
MMF	Mycophenolate mophetil
MTX	Methotrexate
NHS	National Health Service
NSAID	Non-Steroidal Anti-Inflammatory Drugs
OLE	Open-Label Extension
PGA	Physician's Global Assessment
PICO	Population Intervention Comparators Outcomes
Pts	Patients
RA	Rheumatoid Arthritis
SAA	Serum Amyloid A
SD	Standard Deviation
SF-36	Physical Health Summary Questionnaire
SJC	Swollen Joint Count
SZP	Salazopyrin
TJC	Tender Joint Count
TNF	Tumour Necrosis Factor
TOC / TCZ	Tocilizumab
URT	Upper Respiratory Tract
UTI	Urinary Tract Infection
VAS	Visual Analogue Score
W	Week
WBC	White Blood Cells

Appendix 2- Version Control Sheet

Version	Section/ Para/ Appendix	Version/ Description of Amendments	Date	Author/ Amended by
1		1st draft	7 Nov 2016	A More / A Ali
2		2nd draft	30 Nov 2016	A More / A Ali
3				
4				
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