CPAG Summary Report for Clinical Panel – Policy 1609: Anakinra/Tocilizumab for the treatment Adult Onset Still's Disease refractory to second-line therapy(adults)

The Benefits of the Proposition Anakinra/Tocilizumab for the treatment Adult Onset Still's Disease refractory to second-line therapy(adults)			
No	*Outcome measures*	*Grade of evidence*	*Summary from evidence review*
1.	Survival	Not measured	
2.	Progression free survival	Not measured	
3.	Mobility	Not measured	
4.	Self-care	Not measured	
5.	Usual activities	Not measured	
6.	Pain	Not measured	
7.	Anxiety / Depression	Not measured	
8.	Replacement of more toxic treatment	Benefit determined [B]	Prolonged use of corticosteroids especially in high doses can cause severe side effects. The paper by Ortiz Sanjuan et.al (2015) (n=41) reported statistically significant reductions in the doses of prednisolone (P=<0.05) being used in the patient group. This means the results are unlikely to be due to chance. The dose reduced from a median of 20mg/day at baseline to 5mg/day at 1 year. These results should be interpreted with caution. The study design was a retrospective open label multi-centre trial. This study design lacks information on confounding factors. This means that it is difficult to fully attribute the outcomes to the treatment as there is a lack of control over other factors that could influence the outcome being measured. The study participants were from Group 1

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			and Group 2 AOSD but the results presented are pooled so it is not possible to ascertain whether anakinra works better in one or both of the clinical sub-groups. There was no comparison group in the study to compare what changes in symptoms would be seen with standard treatments. Anakinra was prescribed on its own in some patients but also in combination with other drugs for other patients. The results of the study were presented as a single group so it is not possible to fully understand the specific effect that anakinra has made to the symptoms. Follow up was limited to 12 months so there may not have been sufficient time to record medium to long term efficacy and safety of the drug.
9.	Dependency on care giver / supporting independence	Not measured	
10.	Safety	Adverse events identified [B]	In the study by Ortiz-Sanjuan et.al (2015), (n=41) skin reactions were the most common complication reported, with 2 patients discontinuing treatment. In 2 patients treatment had to be discontinued due to severe infections. Other adverse treatment effects reported were leukopaenia (a reduction in white blood cells) and myopathy (muscle disease where the muscle fibres do not function properly). The results should be treated with caution. Anakinra was prescribed on its own in some patients and in combination for others. The results of the study were presented as a single group so it is not possible to fully understand the specific contribution that anakinra has made to the development of side effects. Follow up was limited to 12 months so there may not have been sufficient time to record medium to long term safety of the drug.
11.	Delivery of	Not measured	

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	intervention		

Other health outcome measures determined by the evidence review - anakinra			
No	Outcome measure	Grade of evidence	Summary from evidence review
1.	Resolution of disease symptoms	Grade B	Adult onset Stills Disease (AOSD) leads to numerous symptoms across the body including in the skin, lymph nodes, joints and fever. The study (n=41) (Ortiz-Sanjuan et al 2015)) measured skin symptoms which decreased from being present in 58.5% of patients to 7.3%. Fever decreased from being present in 78% of patients to 22% and swelling of the lymph nodes reduced from 26.8% to 4.9%. Follow up was for 12 months. At 12 months 41.5% of patients still had joint disease. These results should be interpreted with caution for the reasons stated in Section 8. For these specific findings there was no statistical testing undertaken on these clinical findings so it is hard to ascertain the relative significance of the results.
2.	Frequency of disease flares	Grade B	AOSD can be characterised by cycles of symptoms particularly in Group 1 patients. The study showed that out of a total of 28 patients with AOSD 15 patients went into remission at 3 months (Giampetro et al (2013)). These results should be interpreted with caution. The study design was a retrospective questionnaire based study. This study design lacks information on confounding factors. This means

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			that it is difficult to ascertain the outcomes to the treatment as there is a lack of control over other factors that could influence the outcome being measured. It was a very small study so may not have sufficient numbers of patients to detect a real difference if it exists. The retrospective questionnaire design also relies on the information that has been collected by the clinician completing the questionnaire and on their interpretation of the questions. There was no statistical testing undertaken so it is hard to ascertain the scale and significance of the changes seen or whether these may have occurred by chance. The follow up period was 23 months so there may not have been sufficient time to long term efficacy and safety of the drug. The study participants were from Group 1 and Group 2 AOSD but the results presented are pooled so it is not possible to decide whether anakinra works better in one or both of the groups. There was no comparison group in the study to compare what changes in symptoms could be seen with standard treatments. Anakinra was prescribed on its own in some patients but also in combination with other drugs for other patients. The results of the study were presented as a single group so it is not possible to fully understand the specific effect that anakinra has made to the symptoms.
3.	Quality of life	Grade C	The SF-36 is validated generic quality of life measure. Nordstrom et al (2012) (n=22) used the physical health summary of the SF-36 and reported that

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			more patients on anakinra achieved improvement than those on disease modifying anti-rheumatic drugs (DMARDs) (P=0.011). This result was statistically significant. The study design – open, randomised multi-centre allowed comparison with standard therapy. Anakinra was prescribed on its own in some patients but also in combination with other drugs (e.g. steroids and non-steroidal anti-inflammatory drugs (NSAIDs)) for other patients. The results of the study were presented as a single group so it is not possible to fully understand the specific effect that anakinra has made to quality of life.
4.	Normalisation/improvement of ESR and/or ferritin and/or CRP	Grade B	Erythrocyte Sedimentation Rate (ESR) is a non-specific measure of inflammation. C-reactive protein (CRP) is a non-specific measure of inflammation. Ferritin is a protein that stores iron. It is an indirect marker of the total amount of iron stored in the body and is used to diagnose iron-deficiency anaemia. It can also be used as a non-specific marker of inflammation. The study by Ortiz-Sanjuan et al (2015) (n=41) reported the percentage of patients with abnormally elevated CRP reduced from 90.2% to 46.3%, the proportion of patients with a high ESR reduced from 78% to 22% and those with high serum ferritin level reduced from 63.4% of patients to 36.6%. These results should be interpreted with caution for the reasons stated in Section 8. In

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			addition there was no statistical testing undertaken on these clinical findings so it is hard to ascertain the relative significance of the results and whether they could have occurred by chance .
5.	Adherence to treatment	Grade B	Compliance with a treatment regime is essential to achieve the maximum potential benefit. In their study Ortiz-Sanjuan et al (2015) (n=41), reported that after 1 year 14 patients (34%) discontinued anakinra. Anakinra was prescribed on its own in some patients but also in combination for other patients. The results of the study were presented as a single group so it is not possible to fully understand whether the decision to discontinue the drug was due to effects that were solely attributable to anakinra.
6.	Physician global assessment of disease activity	Grade B	A visual analogue scale (VAS) is a measurement instrument that aims to measure intensity or frequency of symptoms. The paper authored by Laskari et al (2011) (n=25) reported at month 3, the 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]). Both these results are statistically significant. The retrospective case series design included a very small cohort of patients not all of whom met the Yamaguchi criteria that is most commonly used to define patients with AOSD. The manner in which the patient characteristics were presented makes it difficult to determine if all patients were refractory to steroids and

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			methotrexate. As data was collected retrospectively it may have been limited by having to rely on patient data available from medical records with incomplete information on the drugs that had been used by the patient before initiating therapy with anakinra. This may lead to confounding bias. 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. Anakinra was prescribed on its own in some patients but also in combination with other drugs for other patients. The results of the study were presented as a single group so it is not possible to fully understand the specific effect that anakinra has made to the symptoms. The study participants were from Group 1 and Group 2 AOSD but the results presented are pooled so it is not possible to decide whether anakinra works better in one or both of the groups.
7.	Normalisation/improvement of anaemia and leucocytosis	Grade B	Anaemia (a lack of red blood cells or the oxygen carrying protein haemoglobin) - specifically iron-deficiency anaemia is common in AOSD. Leucocytosis is an increase in the number of white blood cells and is also a common feature of AOSD. The paper authored by Ortiz-Sanjuan et.al (2015), (n=41) reported a reduction in the percentage of patients with anaemia from 56.1% to 9.8% and the percentage of patients with leucocytosis from 65.9% to 14.6%. These results should be

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			interpreted with caution for the reasons described in Section 8. In addition there was no statistical testing undertaken so it is hard to ascertain the relative significance of the results.

The Benefits of the Proposition –Tocilizumab for the treatment Adult Onset Still's Disease refractory to second-line therapy(adults)			
No	*Outcome measures*	*Grade of evidence*	*Summary from evidence review*
1.	Survival	Not measured	
2.	Progression free survival	Not measured	
3.	Mobility	Not measured	
4.	Self-care	Not measured	
5.	Usual activities	Not measured	
6.	Pain	Not measured	
7.	Anxiety / Depression	Not measured	
8.	Replacement of more toxic treatment	Benefit determined [B]	Prolonged use of corticosteroids especially in high doses can cause severe side effects The study by Cipriani et.al (2014) (n=11) reported prednisolone (steroid) dose was tapered from the baseline median dose of 50mg/day to 12.5mg/day at month 3 and after 12 months 8/11 patients had stopped corticosteroid therapy. These results should be interpreted with caution. The study design is a case series. This type of study design means that there is a lack of information on confounding factors. This means that it is difficult to fully attribute the outcomes to the treatment as there is a lack of control over other factors that could influence the outcome being measured. It was a very small study so may not have

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			sufficient numbers of patients to detect a real difference if it exists. Tocilizumab was prescribed on its own in some patients but also in combination with other drugs for other patients. The results of the study were presented as a single group so it is not possible to fully understand the specific effect that tocilizumab has made to the symptoms. There was no statistical testing undertaken on these clinical findings so it is hard to ascertain the relative significance of the results and whether they could have occurred by chance.
9.	Dependency on care giver / supporting independence	Not measured	
10.	Safety	Adverse events identified [B]	Adverse effects of the treatment range from localised rashes at injection sites to severe infections. Ortiz-Sanjuan et.al (2014) reported that infections were common at 19 months follow up. These results should be interpreted with caution. The study design is an open label multi-centre retrospective observational study. Tocilizumab was used as monotherapy (single drug) in 15 cases and as combination treatment in 19 cases. This makes it difficult to ascertain the specific side effects of tocilizumab in patients with refractory AOSD. Patients were followed up for 1 year which may not have been long enough to ascertain the medium and long term side effects of the drug.
11.	Delivery of intervention	Not measured	

Other health outcome measures determined by the evidence review – Tocilizumab for the treatment Adult Onset Still's Disease refractory to second-line therapy(adults)

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No	Outcome measure	Grade of evidence	Summary from evidence review :
1.	Resolution of disease symptoms	Grade B	Adult onset Stills Disease (AOSD) leads to numerous symptoms across the body including in the skin, lymph nodes, joints and fever. The paper by Ortiz-Sanjuan et.al (2014) (n=34), reported at 1 year that skin symptoms and fever reduced from a prevalence of 58.8% to 5.9%, lymphadenopathy (swelling of the lymph nodes) reduced from being present in 29.4% of patients to 0%. However joint symptoms were resistant to treatment compared to more general symptoms. 32.4% patients had persistent joint involvement after 1 year of therapy. These results should be interpreted with caution for the reasons stated in Section 10. It was a small study so may not have sufficient numbers of patients to detect a real difference if it exists. There was no comparison group in the study to compare what changes in symptoms could be seen with standard treatments. There was no statistical testing undertaken on these clinical findings so it is hard to ascertain the relative significance of the results and whether they could have occurred by chance.
2.	Normalisation/improvement of anaemia and leucocytosis	Grade B	Anaemia (a lack of red blood cells or the oxygen carrying protein haemoglobin) - specifically iron-deficiency anaemia is common in AOSD. Leucocytosis is an increase in the number of white blood cells and is also a common feature of AOSD. The paper by Ortiz-Sanjuan et.al (2014) reported the percentage of patients with leucocytosis decreased from 55.9% to 17.6% and the

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			percentage of patients with anaemia reduced from 44.1% to 2.9%. These results should be interpreted with caution for the reasons stated in Sections 10 and Section 1..
3.	Physician global assessment of disease activity	Grade C	A visual analogue scale (VAS) is a measurement instrument that aims to measure intensity or frequency of symptoms. 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). These results should be interpreted with caution. The study design is a case series. This type of study design means that there is a lack of information on confounding factors. This means that it is difficult to fully attribute the outcomes to the treatment as there is a lack of control over other factors that could influence the outcome being measured. Tocilizumab was prescribed on its own in some patients but also in combination with other drugs for other patients. The results of the study were presented as a single group so it is not possible to fully understand the specific effect that tocilizumab has made to the symptoms.
4.	Subjective symptom scores	Grade C	The SF-36 is validated generic quality of life measure. Puechal et.al (2011) (n=14) reported 60% improvement in the number of tender joints, swollen joints and mean visual assessment score for patients' global health. This prospective cohort study is an observational uncontrolled study. Tocilizumab was prescribed on its own in some patients but also in

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			combination with other drugs for other patients. The results of the study were presented as a single group so it is not possible to fully understand the specific effect that tocilizumab has made to the symptoms There is no comparator group and no randomisation and owing to the small cohort size generalisability of findings to the wider group of patients with AOSD is limited. The lack of statistical testing makes it challenging to determine the significance and scale of the clinical changes seen and whether these have arisen by chance.
5.	Normalisation/improvement of ESR and/or ferritin and/or CRP	Grade B	ESR (erythrocyte sedimentation rate) is a non-specific measure of inflammation. CRP (C-reactive protein) is a non-specific measure of inflammation. Ferritin is a protein that stores iron. It is an indirect marker of the total amount of iron stored in the body and is used to diagnose iron-deficiency anaemia. It can also be used as a non-specific marker of inflammation Ortiz-Sanjuan et.al (2014) reported a reduction in the proportion of patients with elevated ESR from 79.4% to 2.9%, a reduction in the proportion of patients with high CRP from 82.4% to 23% and reduction in the percentage of patients with high serum ferritin levels reduced from 47.1% to 2.9%. These results should be interpreted with caution for the reasons stated in Sections 10 and Section 1.
6.	Adherence to treatment	Grade C	Compliance with a treatment regime is essential to achieve the maximum potential benefit. Cipriani et.al (2014) reported all 11 patients successfully completed

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			treatment with tocilizumab. These results should be interpreted with caution for the reasons highlighted in Section 3. Tocilizumab was prescribed on its own in some patients but also in combination with other drugs for other patients. The results of the study were presented as a single group so it is not possible to fully understand the specific effect that toclilzumab has made to the symptoms and hence compliance.

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