NHS England

Evidence review: Anakinra for periodic fever and auto inflammatory disease

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Evidence review:

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Contents

1. Introduction

This review considers treatment of anakinra for four of the more frequently encountered conditions within the group of periodic fever and auto inflammatory disease.

The conditions for which the treatment anakinra is considered are:

- Familial Mediterranean fever (FMF),
- Hyperimmunoglobulin D Syndrome, (HIDS)/Mevalonate Kinase Deficiency (MKD),
- Tumour necrosis factor receptor–associated periodic syndrome (TRAPS),
- Schnitzler's syndrome

Periodic fever and auto inflammatory diseases are a group of very rare disorders characterized by recurrent episodes of systemic and organ-specific inflammation. The intense episodes of fever and inflammation are caused by an abnormal activation of the innate immune system. The cause is genetic and affects children and adults. Often patients will receive treatments for key symptoms, and invasive exploratory surgical interventions for significant periods of time prior to establishing a defined diagnosis, and / or an effective treatment.

These diseases can also cause amyloidosis, a condition in which insoluble proteins are deposited in the organs and tissues. Systemic AA amyloidosis manifests predominantly as renal failure with high mortality.

The key clinical features of periodic fever and auto inflammatory disease are recurrent episodes of systemic inflammation with disabling fever, overwhelming fatigue and multi-system symptoms including serositis, neutrophilic rash, muco-cutaneous ulcers, arthralgia/arthritis, myalgia, abdominal pain and aseptic meningitis/ headaches.

In addition to clinical features described, studies are lately emerging on the poor quality of life experienced by sufferers, both children and adults, and the impact on education and employment.

The current standard clinical management of the periodic fever and auto inflammatory diseases under consideration aims to suppress the inflammatory response with immune-modulating medication. For some, this can mean high-dose steroid or non-steroidal anti-inflammatory drugs (NSAID) treatment, alongside other disease specific treatments such as colchicine for FMF.

It has been identified that interleukin-1 (IL-1) plays a role in the pathogenesis of inflammation in auto inflammatory disease, thus inhibiting the action of IL-1 using an IL-1 blocking drug is a logical response in control of these disorders. (van der Hilst et al 2016). Anakinra is an IL-1 blocking drug and it is for the treatment of the conditions stated that this review has been undertaken.

It is of note that anakinra is currently commissioned routinely for a range of other immune-mediated conditions: there is an existing policy for the use of anakinra in treating the periodic fever syndrome Cryopyrin Associated Periodic Syndromes (CAPS), and an interim policy for the treatment of Juvenile Idiopathic Arthritis (JIA). In addition, a policy is currently in development for using anakinra in the treatment of Adult Onset Stills Disease (AOSD), but anakinra does not at present have a licence for use for the conditions on which this review is focussed.

Current control methods for specific disease and when anakinra may be considered are as follows:

<u>Familial Mediterranean Fever</u>.

- The first line treatment for FMF is with colchicine. The majority of patients with FMF are controlled on colchicine, which has also shown to be effective in preventing amyloidosis. However there are a minority of patients (5-10%) in whom colchicine is not effective or they are unable to tolerate it. There is also a very small proportion of patients who might develop

amyloidosis despite apparently good response to colchicine.

- The subgroup of patients with FMF who are resistant to colchicine therapy alone (crFMF) or who are unable to tolerate it is the sub-group for whom treatment with anakinra is being considered.

Hyperimmunoglobulin D syndrome (HIDS / Mevalonate Kidney Disease (MKD)

- For patients with frequent episodes of inflammation, treatments can vary and include NSAIDS, high dose steroids, colchicine, and/or etanercept.
- Some studies have shown that targeting IL-1 signalling may be beneficial and is under consideration here for people with a poor response to the usual treatments.

Schnitzler's syndrome

- Conventional therapies such as: antihistamines, NSAID, corticosteroids, immunomodulating agents (colchicine and hydroxychloroquine), and pefloxacin, are used as first line treatments for patients with Schnitzler's syndrome, often patients are treated for symptoms prior to a diagnosis.
- The current treatments usually provide only partial or transient improvement of the symptoms.
- Anakinra would be the treatment under consideration for patients with minimal improvement using first line treatments where there is a possible diagnosis.
- For a probable diagnosis of Schnitzler's syndrome, anakinra may be indicated as the first line treatment

Tumour necrosis factor receptor-associated periodic syndrome (TRAPS)

- For patients with TRAPS the current treatment is usually high-dose steroids and NSAIDS either as an ongoing maintenance dose in chronic cases with constant symptoms, or to manage disease flare-ups. Repeated courses and long term use can cause other issues such as poor response and renal AA amyloidosis. Etanercept is also used for patients with TRAPS but can be ineffective or only partially effective in some patients.
- Anakinra would be considered for patients with a poor response to the first line treatment, and for patients for whom first line treatment is likely to be longer term.

This evidence review assessed the best quality of the minimally available evidence for the management of these four conditions using the IL-1 blocker anakinra.

In some cases with a lack of clear clinical definitions for disease a number of people are treated for undifferentiated auto inflammatory disease. These conditions could reasonably be expected to benefit from the treatment considered in this review, however no studies specific to undifferentiated disease were identified at the literature review.

2. Summary of results

- This evidence review reflects the outcomes for efficacy and safety in the use of anakinra for the specified range of periodic fever and auto inflammatory diseases.
- Nine papers were identified as eligible from the literature search. Of these nine papers
    - three present findings on FMF only
    - one on TRAPS only
    - one on HIDS / MKD only

- one on Schnitzler's only
- four papers present findings on the treatment and management of a range of periodic fever and auto inflammatory disease including: FMF, TRAPS, HIDS/MKD and Schnitzler's syndrome.

- For the purposes of this evidence review where papers are presenting data on a number of conditions the evidence and outcomes are reviewed by condition.
- There are very few high quality trials in the use of anakinra. This is due to the rarity of the periodic fever and auto inflammatory diseases, and of the very small numbers of people with clinically defined disease.
- One study is a randomised control trial (RCT), two are cohort studies, two are systematic reviews and the remaining evidence is in the form of retrospective evaluation of cases. This could present a bias as the cases that are actually written up or submitted for review are more likely be the ones for which treatment was effective.
- Although case studies and retrospective audits are generally considered of lower quality evidence than RCTs, the number of cases showing positive outcomes as a whole is weighty, especially when treatment response is usually quick (a matter of days), and shows a significant improvement or resolution in florid disease.
- Because these are rare conditions and subject to a range of signs and symptoms, the conditions and their outcomes are subject to a degree of clinician and patient interpretation, although laboratory markers of inflammation are also used in most cases reported here.
- The papers consider treatments for adults and children.
- Treatment safety is included to a greater or lesser degree in the papers, however one paper (Rossi-Semerano et al 2015) provides a detail breakdown of adverse events in the use of anakinra, but not by condition. The safety of the treatment can also be inferred from the use of anakinra in other conditions such as CAPS, and in that it is licensed for the treatment of rheumatoid arthritis where it is widely used.
- The most significant adverse events were injection site reactions, and these should be taken in context with the severity of the overall disease.

The key findings for each indication are as follows:

<u>crFMF</u>

- There were six papers contributing to the assessment of anakinra for cr-FMF
- The papers included one randomised controlled trial (RCT) of treatment and control which, although a small sample provided the highest grade evidence of all papers reviewed.
- The studies were reviewed for effectiveness (response to treatment) and for safety.
- Response to treatment includes some or all of the following markers: complete, partial or no response using clinical and inflammatory markers; number of attacks; site of attacks; quality of life; and adverse events.
- The patients in all cases were those resistant or intolerant to the first line of treatment colchicine, i.e.: cr-FMF
- The RCT, which can be taken as the strongest evidence compared two treatment arms of usual treatment and treatment with anakinra and presented a 100% treatment response in the treatment arm (Ben-Zvi et al 2017).
- Using data from all six papers 109 cases out of 114 showed a complete or partial treatment response (Basaran et al 2015; Ben-Zvi et al 2017; ter Haar et al 2013; van der Hilst et al 2016; Ozen et al 2017; Rossi-Semerano et al 2015).
- The publications all consistently report injection site reactions, due to the vehicle of drug delivery, however, the full extent of adverse events (AEs) were not always reported in detail in the publications reviewed.
- To summarize, anakinra appears to be effective for inadequately controlled FMF, i.e.: for patients who do not tolerate or have a poor response to colchicine.

TRAPS

- The evidence from four papers contributed to the review of anakinra in the treatment of TRAPS
- The papers included:
    - one prospective cohort study (Gattorno et al 2008), and
    - three retrospective evaluations of a range of periodic fever and auto inflammatory disorders and outcomes from non IL-1 blockers and with IL-1 blockers (Ozen et al (2017), Ter Haar et al 2013, Rossi-Semerano et al 2016)
- The studies varyingly considered response to treatment by assessing disease activity, response using clinical and inflammatory markers; associated symptoms, duration of attacks, and safety.
- Two papers identified cohorts reflecting both the low penetrance R92Q mutation, and other TRAPS mutations (Ozen et al 2017, Ter Haar et al 2013)
    - All four studies all showed a response to anakinra in the treatment of TRAPS (Gattorno et al 2008, Ozen et al 2017, Ter Haar et al 2013, Rossi-Semerano et al 2016)
- Of particularly compelling evidence was the cohort of five people which showed a relapse when treatment was stopped and improvement when treatment restarted (Gattorno et al 2008)
- Ter Haar et al (2013) reflected that the R92Q mutation responded better to colchicine and NSAID than to anakinra unlike the other genetic forms of TRAPS which had a better response to anakinra, however the data for this were not presented in the publication in detail. This issue would be picked up in criteria for starting and stopping treatment.
- The publications report injection site reactions but the full extent of AEs were often not reported in detail. However, Rossi-Semerano et al (2015) provide detail on adverse events identifying that injection site pain and liver toxicity are more frequent in children receiving anakinra, overall (not just for TRAPS).
- To summarise, anakinra appears to be effective for inadequately controlled TRAPS, although the benefit may be less for patients with the R92Q mutation.

HIDS/MKD

- The evidence from four papers contributed to this review.
- The papers included,
    - a systematic review of 22 papers on the effect of anakinra,
    - three retrospective evaluations of a range of periodic fever and auto inflammatory disorders and outcomes from non IL-1 blockers and with IL-1 blockers
- The studies all reviewed the use of biologics (which includes anakinra), except ter Haar et al (2015) which reviewed outcomes from all treatments - biologics and non-biologics.
- All four publications showed a partial response or complete remission (Kostjukovits et al 2015, Ozen et al 2017, Ter Haar et al 2013, Rossi-Semerano et al 2015).
- The papers showed a greater proportion of people achieving a partial response than a complete response, approximately two thirds partial and one third complete, whereas for cr-FMF and TRAPS a complete response is seen in the greater proportion of patients. However the overall rate of any benefit was still high.
- To summarise, anakinra appears to be effective to some degree for inadequately controlled HIDs, however the proportion of patients achieving complete control is lower than for other conditions.

Schnitzler's syndrome

- The evidence from two retrospective analyses contributed to this assessment of results.
- The papers included:
    - One retrospective analysis of a range of periodic fever and inflammatory disorders of which Schnitzler's syndrome was one, (Rossi Semerano et al 2015), and
    - one which focused on Schnitzler's syndrome only: Neel et al (2014) compared treatment between patients receiving IL-1 blockers and those not receiving IL-1 blockers.
- The publication results showed a dramatic response to anakinra where, in total, only one patient failed to respond (Neel et al 2014, Rossi Semerano et al 2015).
- The analysis from Neel et al (2014) was interpreted as so compelling that the authors suggested that use of anakinra could be diagnostic, and that treatment failure might be indicative of an incorrect diagnosis.
- There were some adverse events, Neel et al 2014, however the participant age was high and the

adverse events were mostly in people with pre-existing conditions (dementia, pre-cancer) so should be considered in this context.
- To summarise, anakinra appears to be effective in treating Schnitzler's syndrome

3. Methodology

- A description of the Population, Intervention, Comparison and Outcomes (PICO) was prepared by NHS England's Policy Working Group and included at section 9
- The PICO was used to determine the search for relevant publications, see section 10.
- Five Literature searches were undertaken to extract evidence on Anakinra, and the diseases: FMF, TRAPS, HIDS/MKD, Schnitzler's syndrome (section 11).
- The abstracts were reviewed to identify papers which were potentially useful, and these were obtained for fuller review according to inclusion / exclusion criteria stated in section 11
- Papers which met the criteria were reviewed in greater detail and the nine papers which provided the highest evidence were included.
- Detailed appraisals were undertaken of the nine papers and recorded in the evidence summary tables in section 7.
- Outcome measures for efficacy and safety for each of the conditions stated with their grade of evidence was reported (section 8).
- Additional papers were used to provide context and particularly in the understanding of safety and these are referenced as appropriate.

4. Results

- This evidence review reflects the outcomes for efficacy and safety in the use of anakinra for the specified range of periodic fever and auto inflammatory diseases.
- Nine papers were identified as eligible from the literature search. Of these nine papers
    - three present findings on FMF only
    - one on TRAPS only
    - one on HIDS / MKD only
    - one on Schnitzler's only
    - three papers present findings on the treatment and management of a range of periodic fever and auto inflammatory disease including: FMF, TRAPS, HIDS/MKD and Schnitzler's syndrome.
- For the purposes of this evidence review where papers are presenting data on a number of conditions the evidence and outcomes are reviewed by condition.
- There are very few high quality trials in the use of anakinra. This is due to the rarity of the periodic fever and auto inflammatory diseases, and of the very small numbers of people with clinically defined disease.
- One study is a randomised control trial (RCT) (Ben-Zvi, et al 2017), two are cohort studies (Basaran et al 2015; Gattorno et al 2008), two are systematic reviews (Kostjukovits et al 2015 van der Hilst et al 2016) and the remaining evidence is in the form of retrospective evaluation of cases (Ozen et al 2017, ter Haar et al 2013, Rossi-Semerano et al 2015, Néel et al 2014)
- This could present a bias as the cases that are actually written up or submitted for review are

more likely be the ones for which treatment was effective

- Although case studies and retrospective audits are generally considered of lower quality evidence than RCTs. The number of cases showing positive outcomes as a whole is weighty, especially when treatment response is usually quick (a matter of days), and shows a significant improvement or resolution in florid disease
- Because these are rare conditions and subject to a range of signs and symptoms, the conditions and their outcomes are subject to a degree of clinician and patient interpretation, although laboratory markers of inflammation are also used in most cases reported here.
- The papers consider treatments for adults and children.
- Treatment safety is included to a greater or lesser degree in the papers, however one paper (Rossi-Semerano et al 2015) provides a detail breakdown of adverse events in the use of anakinra, but not by condition. The safety of the treatment can also be inferred from the use of anakinra in other conditions such as CAPS, and in that it is licensed for the treatment of rheumatoid arthritis where it is widely used.
- The most significant adverse events were injection site reactions, and these should be taken in context with the severity of the overall disease.

Clinical effectiveness considered response to treatment and was measured by clinical signs and symptoms, and by laboratory markers of CRP and SAA levels. The extent of response was measured as a total resolution of signs, symptoms and clinical markers to reflect a complete response, a partial response was a resolution to a greater or lesser degree, and could include resolution of symptoms, but some abnormal laboratory markers, or vice versa, no response or worsening repose was also monitored, alongside time to treatment effect.

Safety outcomes reported on the impact of the mode of administration (subcutaneous injection) and the adverse events associated with anakinra.

In the case of specific conditions results are as follows:

crFMF

Overall response

All patients in the treatment arm of the RCT (Ben-Zvi, et al 2017) showed a complete or atrial benefit in using anakinra for cr-FMF compared to the placebo arm. This reflects the other studies which consistently showed a high positive response in the region of 95% (van der Hilst et al 2016, Rossi-Semerano et al 2015).

Complete response

Ben-Zvi, et al (2017) reported a complete response (i.e. resolution of symptoms and laboratory markers in the normal range) in 7 of 12 patients, again this is consistent with the other reports reflecting a complete response in approximately 76% of patients (van der Hilst et al 2016, Rossi-Semerano et al 2015)

Partial response

A partial response was reported in 5 of 12 patients in the RCT (Ben-Zvi, et al 2017), consistent with approximately 18% in van der Hilst et al (2016) and 2 of 8 patients in Basaran et al (2015) who showed either clinical remission but elevated inflammation markers or normal inflammation markers but partial resolution of symptoms.

No response

Very few people with cr-FMF failed to response, van der Hilst et al (2016) showed a no response in 3 of 64 patients treated with anakinra.

Worsening of symptoms

There were no reports of symptoms worsening as a result of anakinra.

Associated treatment reductions

For cr-FMF Rossi-Semerano et al (2015) reported that 8 patients continued with colchicine treatment with anakinra, but 6 of 9 cases were able to reduce other associated treatments such as high dose steroids.

TRAPS

Complete response

The response to treatment with anakinra is similar in TRAPS to cr-FMF. Gattorno et al (2008) showed that 5 of 5 patients showed complete remission at follow up, and this is similar in other studies. The largest of which was Ter Haar et al (2013) which showed complete remission in 26 of 33 patients.

Partial response

The study of highest quality (Gattorno et al 2008) shows no partial remission since all participants achieved complete remission. The study of greatest number (ter Haar et al 2013) shows partial remission 5 of 33 patients.

Studies which broke down TRAPS by R92Q mutation, and 'other' mutation, suggested that the R92Q mutation did not respond as well to anakinra as the other mutations did (Ozen et al 2017 ter Haar et al 2013).

Of particularly compelling evidence is the speed with which a response was effected, and relapse on withdrawal of treatment: all five patients in the cohort written up by Gattorno et al (2008) showed a response at two days post treatment, four patients relapsed when treatment was stopped and improved when treatment restarted.

No response, Worsening of symptoms

Not reported in the studies reviewed.

HIDS/MKD

Overall response

As for the other conditions there was a high overall response: ter Haar et al (2013) reported that of the 27 patients receiving anakinra 24 showed a partial or complete response. This is similar to Rossi-Semerano et al (2015) where all ten showed a partial or complete response.

Complete response

Unlike for cr-0FMF or TRAPS, where a complete response was shown in most patients, the picture appears reversed for patients with MKS / HIDS, where although most people show a response, fewer show a complete response compared to partial response: ter Haar et al (2013) reported that of the 27 patients receiving anakinra 6 had a complete response. In Rossi-Semerano et al (2015) 3 of 10 showed a complete response. Kostjukovits et al (2015) similarly reported that 19% of cases showed a complete response.

Partial response

ter Haar et al (2013) reported that of the 27 patients receiving anakinra 18 showed a partial response, and Rossi-Semerano et al (2015) reported that 7 of 10 had a partial response.

Kostjukovits et al (2015) similarly reported that 71% of cases showed a partial response.

No response or worsening of symptoms

Was shown in two patients in the systematic review of 33 published cases reported by Kostjukovits et al (2015).

Schnitzler's syndrome

Overall response

Néel et al (2014) reported that 29 patients with Schnitzler's syndrome were treated with anakinra. All experienced improvement within 48 hours. At follow up 24 were in complete remission, five were in partial remission (of which three were asymptomatic).

Complete response

Néel et al (2014) reported that of 29 patients 24 were in complete remission at follow up. Rossi-Semerano et al (2015) reported that of seven patients, one died before follow up so was excluded (of cancer likely related to lifestyle hazards), five had complete response

Partial response

Néel et al (2014) reported that of 29 patients, five were in partial remission (of which three were asymptomatic).

No response

Rossi-Semerano et al (2015) reported that one patient failed to respond to treatment. Neel et al (2014) suggest that no response to treatment could mean that the diagnosis of Schnitzler's syndrome is incorrect, since the response rate is almost total in diagnosed patients and almost immediate with patients experiencing improvement within 48 hours of starting treatment.

Reduction in associated treatments

Where anakinra effects a total or partial response concomitant therapies can be discontinued. Neel et al (2014) reported that 26 of 29 patients discontinued other treatments with three staying on low dose steroids for residual symptoms.

Safety and adverse events

All papers report injection site reactions, and the potential for some more serious adverse events, but did not always provide detail of these by condition. Rossi-Semerano et al (2015) provided the greatest detail of adverse events in using anakinra in their retrospective analysis of 185 patients using anakinra following data request from physician, but did not break this down by disease, so this is reported as overall safety:

Rossi-Semerano et al (2015) outcomes showed:

- minor injection site reactions 39%, which were more frequent in children than adults, 90.2% (CI 77.5-96.1) vs 48% (2 39.9-56.5) p=<0.0001
- injection site pain 36%
- liver enzymes elevation 7%
- weight increase 11%
- respiratory infections 2.8%
- severe infection 9%
- liver toxicity although rare overall, was more frequent in children than adults which appeared to be associated with treatment duration: 17% (CI 8.5-31.3) vs 4.4% (2.0-9.4) p=<0.05

The results of these evaluations suggest that the most common adverse event is injection site reaction or pain, which is to be expected, as is a greater impact for children.

Adverse events by condition are reported as follows:

crFMF

Adverse events

Adverse events were not reported in very much detail except for in Rossi-Semerano et al (2015), see 'safety' results below. However, it is clear that the method of administration by sub cutaneous injection caused the greatest proportion of adverse events in the form of injection site reactions in most people. van der Hilst et al (2016) reported that in 5 of their 64 cases, anakinra was discontinued due to injection site reactions. However, the tolerance of site reactions should be seen in context of the severity of the condition, and these elements were not explored in detail.

TRAPS

Adverse events

All patients' adverse events reported by Gattorno et al (2008) had injection site reactions, but none reported any serious adverse events.

HIDS/MKD

Adverse events

Limited data were presented on specifics of adverse events for patients with HIDS / MKD, although Kostjukovits et al (2015) reported potential for injection site pain, neutropenia, pneumonia, and herpes zoster infection. However Rossi Semerano et al (2015) report on adverse events in patients taking anakinra for a range of conditions, see below.

Schnitzler's syndrome

Adverse events

there were some reports of injection site pain, and six patients developed severe infection, including five with pneumonia, however 4 of these had predisposing conditions of COPD. Of greater relevance is that three patients developed neutropenia, all of which were managed by dosing adjustments (Neel et al 2014).

5. Discussion

- There is limited high quality research on efficacy, tolerability, and safety of the treatment for the periodic fevers in question, this is due to the rare nature of the disease. In addition to the studies reviewed in detail, the review also took into account the high number of single case studies, and the biological plausibility of the use of IL-1 blocking drugs treatments for the conditions under discussion.
- Treatment safety, alongside the results shown in the specific papers presented, can also be extrapolated from the use of anakinra in other conditions such as CAPS, and in that it is licensed for the treatment of rheumatoid arthritis where it is widely used.
- The results are consistent across the papers in showing a benefit for cr-FMF, TRAPS, HIDS/MKD, Schnitzler's syndrome, where Schnitzler's syndrome achieves the greatest complete response rate and HIDS receives the lowest but still clinically significant complete response rate.
- The RCT study for cr-FMF (Ben-Zvi, et al 2017) was the strongest study reviewed.
- The reliance on the large number of retrospective case evaluations can be seen as a limitation, since the data reviewed or submitted in these evaluations are subject to a degree of bias. However the quantity of studies included cannot be ignored, neither can the significance and speed of the treatment response: where treatment achieves a beneficial response this is usually quick (a matter of days), and is seen as a significant reduction in florid disease
- A second limitation is the degree to which there are uniform measures of disease. However the use of clinical and biochemical markers can provide specific measures of impact.
- The implication of the findings suggest that there is a clear benefit to using anakinra to treat periodic fever and auto inflammatory disease that is inadequately controlled by the standard first line treatment.
- In the case of defined disease: Schnitzler's syndrome, there is evidence to support making anakinra the first line treatment.
- Recommendations for further research include understanding further the difference in outcomes for people with TRAPS R92Q, which seems to show a poorer response to anakinra. However this need not affect any policy development as the starting and stopping criteria will indicate appropriate use of the treatment.
- The symptoms of periodic fever and auto inflammatory disease appear to vary in severity, and this severity may play a part in the patient tolerance of the treatment.
- It is not always clear in the papers but where specified, notably for cr-FMF, the colchicine treatment appears to be continued in combination with anakinra (Rossi-Semerano et al 2015).
- While there are some injection site reactions, and a few incidences of serious infection, the use of anakinra seems to be generally well tolerated and results in a high proportion of full or partial remission.
- The publications showed that for the rarer instances of severe side effects such as neutropenia, the effects can be reduced by varying the dose. (Neel et al 2014)
- Although significant side effects appear rare, Rossi-Semerano (2015) analysed the difference of side effects between children and adults. They found that adverse events were significantly higher in children than in adults. Of note, is liver toxicity at 17% is significantly higher than adults at 4.4% (p=<0.05). This appears to be associated with length of time in treatment.

6. Conclusion

- Current non-biologic treatments for periodic fever and auto inflammatory diseases are varyingly effective.
- Some of the conditions stated here are poorly controlled with the usual treatments of high dose steroids, colchicine for FMF, anti TNF treatments and anti-inflammatory treatments for TRAPS, etc.
- The biologic treatment anakinra appears to provide a useful additional treatment option for disease which is poorly controlled by the usual treatments as targets a different inflammatory trigger than the usual current treatments, with good outcomes.
- In the case of some defined disease, such as Schnitzler's syndrome, anakinra may be considered a first line treatment.
- Where there is a treatment effect it is seen very quick, 'turning off' disease within a few days, measured by both clinical signs and symptoms and laboratory markers of inflammation.
- There are some side effects for the use of anakinra. These are mostly related to injection site reaction and pain.
- There are also rarer instances of more serious side effects e.g.: very occasionally neutropenia, and these appear to be managed well with varying the dose.
- Rossi-Semerano et al (2015) undertook analyses between reactions in adults and children and found that children had significantly more frequent adverse event of injection site pain.
- Injection site reactions should be taken in the context of the severity of the overall disease.
- Rossi-Semerano et al (2015), also noted that the rarer side effect liver toxicity was also significantly greater in children than adults at 17% vs 4.4% respectively (p=<0.05). This appears to be linked to length of time in treatment.
- Generally, the side effects are well tolerated and the risk and balance between treatment and side effects will need to be managed on a case by case basis.
- Further reassurances on the safety on anakinra can be extrapolated by the fact that it is licensed for use in other conditions including CAPS and rheumatoid arthritis.
- Specifically for the conditions identified anakinra appears to be of benefit in the following situations:
    - FMF where there is resistance or intolerance to the first line treatment of Colchicine.
    - TRAPS, where there is poorly controlled disease. Although caution should be noted for TRAPS R92Q and starting and stopping criteria should be particularly noted for this mutation.
    - HIDS/MKD, in poorly controlled disease. A smaller proportion of patients achieved complete control in HIDS than in comparison to other conditions reported, however significant numbers achieved partial control.
    - Schnitzler's syndrome, where disease is defined, then anakinra may be considered a first line of treatment.

7. Evidence Summary Table

The evidence summary tables presented use data from studies relating to single conditions but also studies evaluating treatment for a range of conditions. The tables are presented by condition, for example Ozen et al (2017) undertook research which provided outcomes for cr-FMF, TRAPS, and HIDS, so only the relevant data for each sub group is provided in the corresponding evidence table. Table 7.1 stands alone as the only RCT comparing anakinra with a placebo.
Table 7.2 includes the results on anakinra safety presented by Rossi-Semerano et al (2015), although table 7.2 is specifically for crFMF, the safety results are presented by Rossi-Semerano for the whole group with no breakdown by disease.

The tables are as follows:

7.1 Anakinra for Colchicine Resistant Familial Mediterranean Fever compared with Placebo

Study reference	Study Design	Population characteristics	Intervention	Outcome measure type	Outcome measures	Results	Quality of Evidence Score	Applicability	Critical Appraisal Summary
1.Ben-Zvi et al (2017)	P1 – randomised, double blind, placebo controlled trial of patient with cr-FMF	25 patients with CrFMF: 12 to receive anakinra, 13 to receive placebo	Anakinra RCT, intervention and placebo were self-administered with daily injections 100 mg per day, prefilled syringe. Physician exam at time of randomisati	Primary – clinical effectiveness	Overall positive response	12 of 12 (100%)	9	Direct study	• Risk of study bias was low: this was a double blind randomised control trial, with intervention Vs placebo. A small group but well conducted and for a rare disease. • Eligibility (patients with Colchicine resistant FMF) and exclusion criteria were clear • The trial was short term, at 4 months • 7 people, all in the placebo group discontinued due to perceived treatment failure or potential for AE (e.g. pregnancy) • Consistency – the RCT results were consistent with other (less robust) research in the use of anakinra • This was a direct comparison between anakinra and a placebo, both arms of the trial continued to receive their usual medication. • Precision. Although a small sample, with some
					Reduction in attack frequency of greater than >90%	7 patients in anakinra group Significant difference p=0.037			
					Less than 90% reduction in attack frequency	5 patients in anakinra arm			
					Mean no of attacks in all sites	lower in anakinra group: (mean +/- SD 1.7 +/-			

7.1 Anakinra for Colchicine Resistant Familial Mediterranean Fever compared with Placebo									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
			on, twice during study and termination, with weekly nurse communications			1.7 Vs 3.5 +/- 1.9 attacks per pt. per month)			variance in values, the primary and secondary outcomes were significant. • Publication bias. Not applicable to this paper • Large effect. The effect in this trial is significant. • Dose-response relationship. All participants received the same doses, and the study suggests that, based on previous experience with anakinra, a dose escalation may have been beneficial in unresponsive patients • All plausible confounders would have reduced the treatment effect – As a Randomised Control Trial, this study controlled for confounders, although the sample size was small. Conclusion – a small but well conducted RCT that shows clear evidence of significant benefit in reducing overall number of attacks, improving QoL, reducing site specific attacks in joints.
					Comparison and significance of reduction in attacks anakinra Vs placebo Mean of <1 attack per month	6 patients with anakinra Vs 0 patients with placebo Significance P=0.005			
				Secondary – clinical effectiveness	Comparison and significance of attacks in joints, anakinra Vs placebo	Significant difference P=0.019 (CI 0.8 +/- 1.6 Vs 2.1 +/- 1.1)			
					Comparison and significance of attacks in chest / abdomen, anakinra Vs placebo	Insignificant difference. p= 0.3 / 0.38			
					Significance for anakinra Vs Placebo CRP / SAA	p=0.069			
					Significance for anakinra Vs Placebo for Quality of Life (visual analogue score)	significant p=0.045 (CI 7.7 +/- 2.3 Vs 4.2 +/- 2.9)			
				Secondary - safety	Adverse events were not provided in detail in this paper however it was noted that: Injection site reactions mostly due to the vehicle not the drug.	7 placebo group discontinued due to treatment failure in 5, and AE in 2			

7.2 Use of anakinra for the treatment of colchicine resistant familial Mediterranean fever (cr-FMF)									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
2.van der Hilst et al (2016)	R1 - Systematic review of 27 reports of IL-1 treatment in cr-FMF. 22 reports focussed on treatment with anakinra	22 publications on the effect of anakinra in 64 patients. Eligibility were resistance or toxicity to first line treatment: cr-FMF 19 patients had type AA amyloidosis	Systematic review of studies reporting on IL-1 drugs anakinra, canakinumab, and rilonacept since 2006. (This appraisal reflects the results for anakinra)	Primary - clinical effectiveness	Overall response of complete or partial response	95.3%	7	Direct	• Risk of process bias for systematic review is low, however a number of the studies identified in the lit search were single case studies, a limitation is thus which case studies get written and published • Eligibility was clearly identified (cr-FMF, or toxicity). • Consistency – the results monitored complete, partial and no responses, as per numerous studies, and the results were consistent with what we have seen in other studies, although the data presented are limited. • Adverse events were not reviewed in detail in this publication, only where patients discontinued treatment and one possible pneumonia. • Directness of evidence. The systematic review looked at impact of anakinra on cr-FMF • Publication bias. High numbers of case reports included, which will likely bias the result as poor case response may not be written up as a paper. • Large effect. Effective in most patients. • Dose-response relationship was not assessed • Systematic review, not controlled for confounders. Conclusion – a systematic review of available literature, with some potential for publication bias. However the inclusion of larger cohorts and very high effect rates, suggest potential benefit for patients with CR-FMF.
					complete response – no attacks	76.5%			
					Partial response – decrease in attack frequency	18.8%			
					No response	3 patients (sic)			
				Secondary Clinical effectiveness	Observations on type AA Amyloidosis in 19 patients	4 nephrotic syndrome, which showed a decrease in proteinuria after anakinra started.			
						5 pts had anakinra post renal transplant and showed no recurrence of AA amyloidosis.			
						8 pts had end stage renal disease 3 of which had transplantation on anakinra with no recurrence of amyloidosis			
				Secondary Safety	injection site reactions	5 - discontinued due to site reactions			
					pneumonia	1 – possibly related			

7.2 Use of anakinra for the treatment of colchicine resistant familial Mediterranean fever (cr-FMF)									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
3.Basaran et al (2015)	P1 – a prospective cohort study of 8 children with refractory disease	8 children with refractory or colchicine resistant FMF	7 of 8 children started on anakinra, 3 switched to canakinumab, and 1 switched back again. 1 of 8 started on etanercept, switched to anakinra, then to canakinumab. Anakinra dose 1mg/kg/day increased to 3mg/kg/day Constant dosing regimen.	Primary – Clinical effectiveness	Complete response to treatment: no attacks and normal inflammation markers	6 of 8	6	Direct	• Risk of bias: not RCT, not blinded. Low numbers, however, clinical and inflammation markers used to judge outcomes. • Eligibility in trial was for those patients with refractory disease or cr-FMF • No other exclusion or inclusion criteria were provided. • Consistent with expectations. • Direct evidence: Anakinra, for people with refractory disease or cr-FMF • Results based on clear markers • Large effect. All patients benefited • Dose-response relationship. Yes, increased according to lab and clinical remission markers. Conclusion – apparently good response. When anakinra was not sufficient or there was non-compliance patient was switched to canakinumab which is a similar treatment: IL1 blocking agent.
					Clinical remission but elevated inflammation markers Partial response	1 of 8			
					Partial remission, with normal inflammation markers	1 of 8			
				Secondary - Safety	injection site reaction	N/A: 1 on etanercept which resolved after 3 weeks			
4.Ozen et al (2017)	Retrospective case analysis of treatment for 134 people for	27 people treated with biologic agents for FMF of which 14 were	Evaluation of anakinra as first biologic treatment in 14 patients.	Primary Clinical effectiveness	Clinical response of complete normalisation of symptoms	7/14 cases	5	direct	• Potential for bias as submitted cases were physician determined. • In addition there may be differing physician interpretation of disease, • 16 centres submitted data and each centre may work

7.2 Use of anakinra for the treatment of colchicine resistant familial Mediterranean fever (cr-FMF)									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
	three of the conditions under review outcomes for FMF presented in this table	treated with anakinra. Out of Larger study of 134 children and adults, from 16 medical centres. With a confirmed diagnosis of FMF, TRAPS, MKD/HIDS, Treated by a specialist clinician, between 2008 and 2012, with a defined level of inadequate disease control thus eligible for biologic therapy, for whom there is a minimum of 12 month follow up	No dosing regimen given, or information on intermittence or continuous treatment		Biochemical control of normal levels of CRP /SAA	6/14 cases			to different protocols and have populations. • Detail of AE not given in study write up. Discontinuation reported as lack of efficacy or undefined side effects • Complex data presentation and interpretation of treatment for a range of conditions and impossible to extract full detail required with presented data. • Treatment outcomes were not published for canakinumab or if enrolled on an international trial due to conflict of interest • Eligibility for trial is clear: patients with refractory disease, poor control, between 2008 and 2012. • Consistency: the reported results appeared consistent with other case studies. • Directness of evidence: case reviews of patients with biologic treatments for poorly managed disease. • Precision. There is a lack of independent measure for determining severity of disease and efficacy of treatment • Publication bias. Not clear whether all cases were submitted for review. • Dose-response relationship. Continuous vs intermittent use not analysed. Conclusion – Difficult data presentation to extract information from, and some query regarding discrepancy of data. Some questions remain unanswered regarding outcomes and AE.
5.Ter Haar et al (2013)	Retrospective evaluation of 496 patients on the eurofever registry, of which	Three patients with FMF treated with anakinra from study of 496 patients (children and adults) from 77 centres in	Study evaluated all treatments used in the conditions. All cases were validated and those where response to	Primary – clinical effectiveness	Complete remission, no sign of active disease, normalised inflammatory markers and allowing for persistence of sequelae	3 of 3	6	Direct	• Very small sub group of this larger study received anakinra for FMF. • Risk of bias: Those achieving complete remission might not have been followed up and not included in study. However, extensive study showing real life information and management of cases included. • Eligibility – inclusion criteria for patients used but not presented in the paper and inclusion criteria for literature reviewed also specified.

7.2 Use of anakinra for the treatment of colchicine resistant familial Mediterranean fever (cr-FMF)									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
	treatment with anakinra for FMF was a sub group.	33 countries. local physicians provided anonymised retrospective information on patients with: FMF; CAPS; TRAPS; MKD/JIDS; PAPA; DIRA; NLRP12, PFAPA. Inclusion criteria were specified but not provided.	treatment was recorded were used All treatments were evaluated. Added to this was a literature review of data using prospective trials or trials > 5 patients.						• Consistency: results generally consistent with known information, some inconsistency between analysis and lit review, possibly due to selection bias, • Directness of evidence. Evaluation of full treatment schedule for conditions presented. • Precision. Not always clear definitions of complete or partial remission, or minimum duration of remission. • Publication bias. Potential for some publication bias affecting studies reviewed • No CIs / significance reported • Dose-response relationship. Not discussed in detail, often variable for all treatments. Conclusion – useful summary of data available to provide an overarching picture of anakinra which will help develop treatment guidelines for anakinra, but small group for this condition.
6.Rossi-Semerano. et al (2015)	Retrospective analysis of 189 patients following data request from physician.	13 patients with FMF as part of a larger study of 189 French patients (adults and children) from 38 centres with: FMF, CAPS, AOSD, gout, systemic juvenile idiopathic arthritis, MKD	Anakinra in 185 patients (at least once), most with daily injections (a few on demand). Adults received 100 mg, children 1-6mg/kg/day	Primary - clinical effectiveness	Complete response to anakinra as determined by signs of active disease, inflammation markers and CRP levels	6/13 (46.2%)	6	Direct and indirect	• Risk of bias: retrospective and not standardised evaluation of disease • Eligibility: clearly stated adults and children who received IL-1 blocking drug, but unclear whether physicians included all their cases – potential for selection bias. • Consistency. Consistent approach to evaluation of results • Direct evidence to this review, also included other similar disease outcomes • Precision. Clear data collection and analysis • Publication bias. Possible see above • Large effect. • Dose-response relationship. Not well discussed, variation between adults and children. • Adverse events, described and recorded in detail but
					partial response	6/13 (46.2%)			
					no response	1/13 (7.6%)			
					Associated treatment reduction (ATR)	6/9 (66.7%)			
				Secondary: reasons for withdrawal	no withdrawal	6/13			
					loss of efficacy or ineffective	1/13			

7.2 Use of anakinra for the treatment of colchicine resistant familial Mediterranean fever (cr-FMF)									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
		treated with an off-label IL-1 blockers	25 used canakinumab (limited information collected) as second line after anakinra. 8 patients with FMF received colchicine with anakinra		Adverse event	3/13			reflect the overall group's adverse outcomes, not just for the subgroup of cr-FMF patients. Conclusion – comprehensive study reviewing many cases covering the diseases of interest and others. Data could help development of treatment guidelines, as in other reports analysis of case studies will be subject to some bias.
					Patient request	1/13			
					on demand treatment	1/13			
					switch to canakinumab	3/13			
				Secondary outcomes: Safety – *NB data reflects safety outcomes for whole study not just sub group*	minor injection site reactions	39% more frequent in children than adults 90.2% (CI 77.5-96.1) vs 48% (2 39.9-56.5) p=<0.0001			
					injection site pain	36%			
					liver enzymes elevation	7%			
					weight increase	11%			
					respiratory infections	2.8%			
					severe infection	9%			
					liver toxicity associated with treatment duration	more frequent in children than adults 17% (CI 8.5-31.3) vs 4.4% (2.0-9.4) p=<0.05			

7.3 Use of anakinra for the treatment of TRAPS									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**

7.3 Use of anakinra for the treatment of TRAPS									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
7.Gattorno et al (2008)	P1 – primary research – a prospective cohort study	4 children, 1 adult with poorly controlled TRAPS requiring high dose steroids. Of the 5 cases 3 patients had recurrent disease with prolonged and frequent attacks, and 2 patients had chronic disease and constant symptoms	Daily anakinra: 1.5mg/kg/day. Stopped at day 15. Assessment of disease activity (VAS) on day 0, 3, 7, 15, at disease relapse, then monthly Restarted in the event of new disease flare. Patients with recurrent disease did not receive concurrent steroids. Patients , with chronic disease maintained normal dosage of steroids Follow up (mean 11.4 mths, range 4-20 mths),	Primary – clinical effectiveness	overall response – complete and partial	5 of 5	(7)	Direct	• Risk of bias: not RCT, not blinded. Low numbers, however, serum levels tested and fever or not is a binary measure. • Eligibility in trial was for those patients with poorly controlled TRAPS, but no information provided in exclusion or inclusion criteria apart from that. • Consistency – the results were fairly robust and consistent in monitoring outcomes and impact of withdrawal and relapse • Adverse events were injection site reactions • Directness of evidence. The trial looked at impact of anakinra in people for whom there is no apparent working alternative other than maintenance of steroids and NSAIDS. • Precision. Results based on clear outcomes • Publication bias. Not relevant for this trial • Large effect. 'Dramatic response' in all patients. • Dose-response relationship. Mg per kg • Of compelling evidence in support of the effect of anakinra was the withdrawal of treatment, subsequent relapse, and response following reintroduction of treatment. 100% relapsed at between 3-8 days and 100% showed 'prompt improvement' on reintroduction of treatment. Conclusion – apparently good response
					Complete response of No episodes of fever at follow up	5 of 5			
					Partial response to treatment	0 of 5			
					Serum levels of C-reactive protein and SAA in the normal range	100%			
					Reduction in associated treatments	100%			
				Secondary - safety	Skin reactions at injection site	100%			
					Serious adverse events	0			

7.3 Use of anakinra for the treatment of TRAPS									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
									evidencing short term and longer term efficacy and safety of anakinra: a valid alternative for patients on long term steroids or whose condition limits their daily activities severely.
8.Ozen et al (2017)	Retrospective case analysis of treatment for 134 people for three of the conditions under review	Of 47 TRAPS patients treated: 2 patients in the R92Q cohort treated with anakinra 15 patients in cohort 2 (non R92Q mutation) were treated with anakinra. From the larger study of 134 children and adults, from 16 medical centres. With a confirmed diagnosis of FMF, TRAPS, MKD/HIDS, Treated by a specialist clinician, between 2008 and 2012, with a defined level of inadequate disease control thus eligible for biologic therapy, for whom there is a minimum of 12 month follow up	17 patients in 2 cohorts all showing inadequate disease control. It is not clear from the paper the dose regime	Primary clinical effectiveness	Cohort one (R92Q) - complete clinical and biochemical response	1 of 2 patients	5	Direct	• Potential for bias – physician submitted cases and differing physician interpretation of disease, • 16 centres submitted data and each centre may work to different protocols and have populations. • Detail of AE not given in study write up. Discontinuation reported as lack of efficacy or undefined side effects • Complex data presentation and interpretation and impossible to extract full detail required with presented data. • Eligibility for trial is clear: patients with refractory disease, poor control, between 2008 and 2012. • Consistency: the overall results appeared consistent with other case studies. • Directness of evidence: case reviews of patients with biologic treatments for poorly managed disease. • Precision. There is a lack of independent measure for determining severity of disease and efficacy of treatment • Publication bias. Not clear whether all cases were submitted for review. • Dose-response relationship.
					Cohort two - complete clinical response compared to etanercept	'More likely' P=0.03 the numbers specific to anakinra were not provided, but analysis was provided that showed patients on anakinra were significantly more likely to have complete clinical and biochemical response to anakinra than to etanercept			

7.3 Use of anakinra for the treatment of TRAPS									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
					Cohort two - complete biochemical response compared to etanercept	'More likely' P=0.01 the numbers specific to anakinra were not provided, but analysis was provided that showed patients on anakinra were significantly more likely to have complete clinical and biochemical response to anakinra than to etanercept			Continuous vs intermittent use not analysed. Conclusion – Difficult data presentation to extract information from, and some query regarding discrepancy of data. Some questions remain unanswered regarding outcomes and AE, however bottom line results reported. Treatment outcomes not recorded for canakinumab or if enrolled on an international trial
9.Ter Haar et al (2013)	Retrospective evaluation of 496 patients on the eurofever registry with results of literature review presented	33 patients with TRAPS were treated with anakinra from the larger study of 496 patients (children and adults) from 77 centres in 33 countries. local physicians provided anonymised	The evaluation reviewed and evaluated all treatments used in the conditions identified. All cases were validated and those where response to treatment was	Primary - clinical effectiveness	Complete remission	26 / 33 patients	6	Direct	• Part of larger study • Risk of bias: Those achieving complete remission might not have been followed up and thus not included in study. However, extensive study showing real life information and management of cases included. • Eligibility – inclusion criteria for patients used but not presented in the paper and inclusion criteria for
					partial remission,	5 / 33 patients			
					failure	Not stated			

7.3 Use of anakinra for the treatment of TRAPS									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
		retrospective information on patients with: FMF; CAPS; TRAPS; MKD/JIDS; PAPA; DIRA; NLRP12, PFAPA. Inclusion criteria were specified but not provided.	recorded were used Added to this was a literature review of data using prospective trials or trials > 5 patients. The response to anakinra is reported here.		Worsening.	Not stated			literature reviewed also specified. • Consistency: results generally consistent with known information, some inconsistency between analysis and lit review, possibly due to selection bias, • Direct evidence, evaluating treatment for conditions presented. • Precision. Not always clear definitions of complete or partial remission, or minimum duration of remission. • Publication bias. Potential for some publication bias affecting studies reviewed • No CIs / significance reported • Dose-response relationship. Not discussed in detail, often variable for all treatments. • Paper reported that R92Q mutation responded better to colchicine and NSAIDS, than other types of TRAPS did, however the data were not presented in detail. Conclusion: a useful summary of data available to provide an overarching picture of anakinra which will help develop treatment guidelines for anakinra.

7.3 Use of anakinra for the treatment of TRAPS									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
10.Rossi-Semerano et al (2015)	Retrospective analysis of 189 patients following data request from physician.	3 patients with TRAPS evaluated as part of a wider study of 189 patients from 38 centres with: FMF, TRAPS, CAPS, AOSD, gout, systemic juvenile idiopathic arthritis, MKD treated with an off-label IL-1 blockers	Evaluation of data for patients with TRAPS treated with anakinra Dosing regimen not clear for these patients, but overall most had daily injections (a few on demand). Adults received 100 mg, children 1-6mg/kg/day	Primary – clinical effectiveness	Overall positive response	3/3	6	Direct and indirect	• Risk of bias: retrospective and not standardised evaluation of disease • Eligibility: clearly stated adults and children who received IL-1 blocking drug, but unclear whether physicians included all their cases – potential for selection bias. • Consistency. Consistent approach to evaluation of results • Adverse events, described and recorded in detail. • Direct evidence to this review, also included other similar disease outcomes • Precision. Clear data collection and analysis • Publication bias. Possible see above • Large effect but small group. • Dose-response relationship. Not well discussed, variation between adults and children. Conclusion – comprehensive study reviewing many cases covering the diseases of interest and others. Data could help development of treatment guidelines, as in other reports analysis of case studies will be subject to some bias.
					Complete, response	1			
					partial response	2			
					failure to respond	0			
					Associated treatment reduction (ATR)	2/3			
				Secondary outcomes: Safety – *NB data reflects safety outcomes for whole study not just sub group*	minor injection site reactions	39% more frequent in children than adults 90.2% (CI 77.5-96.1) vs 48% (2 39.9-56.5) p=<0.0001			
					injection site pain	36%			
					liver enzymes elevation	7%			
					weight increase	11%			
					respiratory infections	2.8%			
					severe infection	9%			
					liver toxicity associated with treatment duration	more frequent in children than adults 17% (CI 8.5-31.3) vs 4.4% (2.0-9.4) p=<0.05			

7.4 Use of anakinra for the treatment of HIDS / MKD									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
11.Kostjukovits et al (2015)	R1 – systematic review of 33 published case studies	33 published case studies on paediatric HIDS patients treated with biological medicine. 21 treated with Anakinra, and 16 with etanercept. Eligibility = <18 years old, with biologic treatment and genetically confirmed HIDS. Duplicates excluded	Review of published cases evaluating biologic treatments etanercept and anakinra (and 5 with canakinumab) Continuous treatment in all but 4 people who dosed on demand Varying dose regime. Reported here is response to anakinra in 21 patients	Primary Clinical effectiveness	Complete or partial response to anakinra	19 (90%)	5	direct	• Risk of bias for systematic review is low, however a number of the studies were single case studies and thus review is based on which get written and published • Eligibility was clearly identified • The results were presented clearly, • Outcomes monitored for both etanercept and anakinra. • Adverse events were not reviewed in any detail. • Directness of evidence: The systematic review looked at impact of anakinra on HIDS in children. • Precision. Results largely based on poorer quality evidence (published case studies). • Publication bias. High numbers of case reports included, which will likely bias the result as poor case response may not be written up as a paper. • Large effect. Effective in most patients. • Dose-response not clearly assessed Conclusion – a systematic review of available literature, with some potential for publication bias and variation in clinical management. However, as far as this review goes, there appears to be good outcomes from using biologics including anakinra, in treating HIDS early.
					Complete resolution	4 (19%)			
					Partial resolution or Positive	15 (71%)			
					No change	1 (5%)			
					Worsening of symptoms	1 (5%)			
				Secondary outcomes	Adverse events:	No data provided on numbers but paper reported potential for pain at injection site, neutropenia, bacterial pneumonia, Herpes zoster infection.			

7.4 Use of anakinra for the treatment of HIDS / MKD									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
12.Ozen et al (2017)	Retrospective case analysis of treatment for 134 people. Treatment outcomes not recorded for canakinumab or if enrolled on an international trial.	31 cases of HIDS treated with biologics of which 21 were treated with anakinra as first line, from a larger study of 134 children and adults, from 16 medical centres. With a confirmed diagnosis of FMF, TRAPS, MKD/HIDS. Patients treated by a specialist clinician, between 2008 and 2012, with a defined level of inadequate disease control thus eligible for biologic therapy, for whom there is a minimum of 12 month follow up	Retrospective review of outcomes in 21 cases treated with anakinra.	Primary Clinical effectiveness	Clinical control with anakinra	11 (52%)	5	direct	• Potential for bias – physician submitted cases and differing physician interpretation of disease, • 16 centres submitted data and each centre may work to different protocols and have populations. • Detail of AE not given in study write up. Discontinuation reported as lack of efficacy or undefined side effects • Complex data presentation and interpretation and impossible to extract full detail required with presented data. • Eligibility for trial is clear: patients with refractory disease, poor control, between 2008 and 2012. • Consistency: the overall results appeared consistent with other case studies. • Directness of evidence: case reviews of patients with biologic treatments for poorly managed disease. • Precision. There is a lack of independent measure for determining severity of disease and efficacy of treatment • Publication bias. Not clear whether all cases were submitted for review. • Dose-response relationship. Continuous vs intermittent use not analysed. Conclusion – Difficult data presentation to extract information from, and some query regarding discrepancy of data. Some questions remain unanswered regarding outcomes and AE, however bottom line results reported (see results column).
					Biochemical control with anakinra	9 (43%)			
					Clinical response with anakinra compared to etanercept	p=0.08 clinical control (not statistically significant)			
					Biochemical control with anakinra compared to etanercept	p=0.12 for biochemical control			

7.4 Use of anakinra for the treatment of HIDS / MKD									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
									Treatment outcomes not recorded for canakinumab or if enrolled on an international trial
13.Ter Haar, N. et al (2013)	Retrospective evaluation of 496 patients on the eurofever registry with additional literature review presented.	67 patients with MKD of which 27 were treated with anakinra, from a larger study of 496 patients (children and adults) from 77 centres in 33 countries. local physicians provided anonymised retrospective information on patients with: FMF; CAPS; TRAPS; MKD/HIDS; PAPA; DIRA; NLRP12, PFAPA. Inclusion criteria were specified but not provided here.	Study evaluated all treatments: IL-1 blocking drugs, NSAIDS, Corticosteroids, colchicine, TNF blockades, other usual treatment All cases were validated and those where response to treatment was recorded were used.	Primary – Clinical effectiveness	Overall effective response to treatment	24 of 27 patients	6	Direct	• Risk of bias: Those achieving complete remission might not have been followed up therefore not included in study. However, extensive study showing real life information and management of cases included. • Eligibility – inclusion criteria for patients specified, and inclusion criteria for literature reviewed also specified. • Consistency: results generally consistent with known information, some inconsistency between analysis and lit review, possibly due to selection bias, • Directness of evidence. Evaluation of full treatment schedule for conditions presented. • Precision. Not always clear definitions of complete or partial remission, or minimum duration of remission. • Publication bias. Potential for some publication bias affecting studies reviewed • No CIs / significance reported • Dose-response relationship. Not discussed in detail, often variable for
					Complete remission	6			
					partial remission	18			
					failure	Not reported			
					Worsening	Not reported			

7.4 Use of anakinra for the treatment of HIDS / MKD									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
									• all treatments. • The paper concluded that in comparing treatments a sizeable proportion are adequately controlled with corticosteroids, but that poorly controlled HIDS/MKD may benefit from IL-1 blocking agents. Conclusion – useful summary of data available to provide some information to help develop treatment guidelines for anakinra, as second line therapy
Rossi Semerano et al (2015)	Retrospective analysis of 189 patients following data request from physician.	10 patients with HIDS / MKD treated with anakinra as sub group from larger study of 189 French patients – adults and children - from 38 centres with: FMF, CAPS, AOSD, gout, systemic juvenile idiopathic arthritis, MKD treated with an off-label IL-1 blockers	Review of data for 185 patients most with daily injections (a few on demand). Adults received 100 mg, children 1-6mg/kg/day .	Primary outcome clinical effectiveness	Complete response	3/10	6	Direct and indirect	• Risk of bias: retrospective and not standardised evaluation of disease • Eligibility: clearly stated adults and children who received IL-1 blocking drug, but unclear whether physicians included all their cases – potential for selection bias. • Consistency. Consistent approach to evaluation of results • Adverse events, described and recorded in detail. • Direct evidence to this review, also included other similar disease outcomes • Precision. Clear data collection and analysis • Publication bias. Possible see above • Large effect. • Dose-response relationship. Not well discussed, variation between adults and children. Conclusion – comprehensive study reviewing many cases covering the diseases of interest and others. Data could help development of treatment
					partial response	7/10			
					failure to respond	0/10			
					Associated treatment reduction (ATR)	3/3 (the 3 with complete remission)			
					withdrawals	7/10			
					Inefficacy or subsequent loss of efficacy	2/10			
				Secondary outcome - safety	Adverse events	2/10			
				Secondary outcomes: Safety – *NB data reflects safety outcomes for whole study not just sub group*	minor injection site reactions	39% more frequent in children than adults 90.2% (CI 77.5-96.1) vs 48% (2 39.9-56.5) p=<0.0001			
					injection site pain	36%			

7.4 Use of anakinra for the treatment of HIDS / MKD									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
					liver enzymes elevation	7%			guidelines, as in other reports analysis of case studies will be subject to some bias.
					weight increase	11%			
					respiratory infections	2.8%			
					severe infection	9%			
					liver toxicity associated with treatment duration	more frequent in children than adults 17% (CI 8.5-31.3) vs 4.4% (2.0-9.4) p=<0.05			

7.5 Use of anakinra for the treatment of Schnitzler's syndrome									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
Neel, A et al (2014)	Retrospective analysis of cases from multi-centre (France)	42 adult patients with Schnitzler's syndrome. mean age of disease onset 59.9 (+/-11.9) Recruited from 16 centres, 30 men 12 women. No significant difference between characteristics of patients on IL1Ra or No IL-1Ra, except slightly elevated pain scores in those who received IL-1Ra All had active disease at some sort at the point of IL-1 introduction, 24 had failed immunomodulating, immunosuppressive, or non anti-IL-1 treatment	42 patients' data analysed 29 treated with anakinra (of which one switched to canakinumab) Of which 19 received intermittent anakinra and 10 daily anakinra 13 patients did not receive IL-1Ra Last follow up (median 6 mths, range 3-79 mths)	Primary – clinical effectiveness	Overall benefit of >50% improvement	29 of 29	7	Direct	• Risk of bias: If symptoms cleared then the patients may not have been included in the study; • Patients were recruited from medical departments and did not include dermatology referrals so may overestimate burden of disease. • Patients were older –mean age 59.9 with 4 deaths, 77, 77, 80 and 86. • Eligibility: cases were included if they met specified criteria of disease but these criteria were not stated in the paper • Consistency: results and cases appeared consistent with what we know • Adverse events: reported and consistent with what we know. The severe AEs have to be taken in context with the pre-existing conditions and age of patients. • Directness of evidence: all applicable • Precision: clinical assessment based on laboratory markers of anaemia, CRP levels, and also symptom assessments of moderate severe, mild etc.
					Complete remission of disappearance of all clinical signs of disease	24 of 29			
					Partial remission, improvement of at least 50% Including CRP levels	5 of 29 (of these 3 had mild residual bone pain)			
					Time to treatment effect	48 hrs of starting IL-1R			
					Dosing regime	Only 4 with intermittent anakinra achieved complete remission, daily injections had to be resumed for the others.			
					Discontinued concomitant therapies	26 of 29			
				Primary outcomes - safety	Neutropenia	3 – all of which resolved with varying the dose			
					Severe infection	6, of which 5 had predisposing factors			

7.5 Use of anakinra for the treatment of Schnitzler's syndrome									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
					Injection site reactions	5			• Large effect: significant impact of IL-1 reported • Dose-response relationship: yes: constant use achieved complete remission more frequently than intermittent use, and adjusting the dose addressed some of the side effect of neutropenia. Conclusion: IL-1Ra appears effective in Schnitzler's syndrome, so much so that treatment failure (anakinra) may indicate incorrect diagnosis. Appears safe and effective in long term treatment, side effects are tolerable for disease management. 4 deaths but not thought to be linked to anakinra as predisposing conditions and age range 77-86 yrs
Rossi-Semeran o et al (2015)	Retrospective analysis of 189 patients following data request from physician.	189 French patients – adults and children - from 38 centres with: FMF, CAPS, AOSD, gout, systemic juvenile idiopathic arthritis, MKD treated with an off-label IL-1 blockers	Anakinra in 185 patients (at least once), most with daily injections (a few on demand). Adults received 100 mg, children 1-6mg/kg/day	Primary – clinical effectiveness	Complete response	5 of 7 patients	6	Direct and indirect	• Risk of bias: retrospective and not standardised evaluation of disease • Eligibility: clearly stated adults and children who received IL-1 blocking drug, but unclear whether physicians included all their cases – potential for selection bias. • Consistency. Consistent approach to evaluation of results • Adverse events, described and recorded in detail. • Direct evidence to this review, also included other similar disease
					partial response	0 / 7			
					failure to respond	1 / 7			
					Associated treatment reduction (ATR)	5/6 ATR			

7.5 Use of anakinra for the treatment of Schnitzler's syndrome									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
			25 used canakinumab (limited information collected) as second line after anakinra.	Secondary outcomes: Safety – *NB data reflects safety outcomes for whole study not just sub group*	minor injection site reactions	39% more frequent in children than adults 90.2% (CI 77.5-96.1) vs 48% (2 39.9-56.5) p=<0.0001			outcomes • Precision. Clear data collection and analysis • Publication bias. Possible see above • Large effect. • Dose-response relationship. Not well discussed, variation between adults and children. Conclusion – comprehensive study reviewing many cases covering the diseases of interest and others. Data could help development of treatment guidelines, as in other reports analysis of case studies will be subject to some bias.
					injection site pain	36%			
					liver enzymes elevation	7%			
					weight increase	11%			
					respiratory infections	2.8%			
					severe infection	9%			
					liver toxicity associated with treatment duration	more frequent in children than adults 17% (CI 8.5-31.3) vs 4.4% (2.0-9.4) p=<0.05			

8. Grade of evidence table

The grade of evidence tables, as for section 7, are presented by condition, reflecting outcome measures with the best available evidence.

8.1 Use of Anakinra to treat cr-FMF compared to placebo

Outcome Measure	Reference	Quality of Evidence Score	Applicability	Grade of Evidence	Interpretation of Evidence
Overall response to anakinra compared to placebo	Ben-Zvi et al (2017)	9	Direct	Grade A	This outcome measure of overall response to anakinra shows the number of people in the treatment arm (receiving anakinra) who experienced a positive outcome and compares this to the response in the control arm (the placebo). A positive outcome includes a complete or partial resolution of disease, where complete is better than 90% improvement and partial is less than 90%. The best study for this outcome measure is identified as a double bind randomised control trial by Ben-Zvi et al (2017), although this is a small study the results are of high quality. • All patients in the treatment arm reported a complete or partial benefit. • In comparison, 7 patients on the placebo arm withdrew from treatment, 5 due to treatment failure and 2 for potential AEs (pregnancy and allergy). There is clear evidence of significant benefit to patients with cr-FMF, where this study shows a benefit to 100% of participants. The uncertainties of this result are minimal. Although the sample size was fairly small, the assumptions used to calculate the sample size to a power of 80% were modified during the trial to reflect actual data not assumed data, which provides increased confidence in the results. A randomised control trial is considered high quality evidence, and this was a blinded RCT so no members of the trial knew if they were on the placebo or the treatment arm, thus responses are controlled for confounders. The trial was short term, at 4 months which reflects the speed at which the treatment benefits are achieved. However, longer term effects could not be studied. All participants received the same dose of placebo or anakinra, and thus it is not possible to identify if a poorer response may have been improved by a dose escalation. The study results were broadly consistent with other research, although retrospective analyses of greater numbers show a 95% improvement rather than a 100% improvement (van der Hilst 2016) as per table 8.2.

8.1 Use of Anakinra to treat cr-FMF compared to placebo					
					This was a small but well conducted RCT that shows clear evidence of significant benefit in reducing overall number of attacks, improving QoL, reducing site specific attacks in joints.
Reduction in attack frequency of greater than 90%	Ben-Zvi et al (2017)	9	Direct	Grade A	This outcome measure of complete response to anakinra shows the number of people in the treatment arm (receiving anakinra) who experienced a greater than 90% reduction in attacks. The best study for this outcome measure is identified as a double bind randomised control trial by Ben-Zvi et al (2017), although this is a small study the results are of high quality. The outcome measure of complete response to treatment reported that: • 7 of 12 patients had >90% reduction in attack frequency There is clear evidence of significant likelihood of complete remission of disease following treatment with anakinra compared to the placebo, showing a significance of p=0.037 (reduction in attack frequency). The uncertainties of this result are minimal. Although the sample size was fairly small, the assumptions used to calculate the sample size to a power of 80% were modified during the trial to reflect actual data not assumed data, which provides increased confidence in the results. A randomised control trial is considered high quality evidence, and this was a blinded RCT so no members of the trial knew if they were on the placebo or the treatment arm, thus responses are controlled for confounders. The trial was short term, at 4 months which reflects the speed at which the treatment benefits are achieved. However, longer term effects could not be studied. This was a small but well conducted RCT that shows clear evidence of significant benefit in reducing overall number of attacks, improving QoL, reducing site specific attacks in joints.
Partial response, - improvement but less than less than a 90% reduction in attack frequency	Ben-Zvi et al (2017)	9	Direct	Grade A	This outcome measure of partial response shows the number of people in the treatment arm (receiving anakinra) who experienced a positive outcome of less than 90% reduction in attacks. The best study for this outcome measure is identified as a double bind randomised control trial by Ben-Zvi et al (2017), although this is a small study the results are of high quality. The outcome measure of partial response to treatment (measured as a response but less than 90% reduction in attacks) reported that: • 5 of 12 patients had a partial response. There is clear evidence of some benefit to patients with cr-FMF, however, all participants received the same dose of placebo or anakinra, and thus it is not possible to identify if a partial response may have been improved by a dose escalation The uncertainties of this result are minimal. Although the sample size was fairly small, the assumptions used to calculate the sample size to a power of 80% were modified during the trial to reflect actual data not assumed data, which provides increased confidence in the results. A randomised control trial is considered high quality evidence, and this was a blinded RCT so no members of the trial knew if they were on the placebo or the treatment arm, thus responses are controlled for confounders. The trial was short term, at 4 months which reflects the speed at which the treatment benefits are achieved. However, longer term effects could not be studied.

8.1 Use of Anakinra to treat cr-FMF compared to placebo					
					The study results were broadly consistent with other research. This was a small but well conducted RCT that shows clear evidence of significant benefit in reducing overall number of attacks, improving QoL, reducing site specific attacks in joints.
Mean number of attacks in treatment arm Vs control arm	Ben-Zvi et al (2017)	9	Direct	Grade A	This outcome measure of mean number attacks was used to understand the number of attacks in treatment vs control. Since FMF is characterised by periodic attacks of inflammation, understanding the reduction of these is vital to understand efficacy of treatment. The best study for this outcome measure is identified as a double bind randomised control trial by Ben-Zvi et al (2017), although this is a small study the results are of high quality. The results analysed mean number attacks in the treatment arm compared to the placebo. • The mean number of attacks was lower in anakinra group (mean +/- SD 1.7 +/- 1.7 Vs 3.5 +/- 1.9 attacks per pt. per month) • 6 patients in the anakinra arm had a mean of <1 attack per month compared with 0 patients in the placebo arm. There is clear evidence of a significant reduction in attack rate for the participants receiving anakinra. Half the participants experienced fewer than 1 attack a month on treatment The uncertainties of this result are minimal. Although the sample size was fairly small, the assumptions used to calculate the sample size to a power of 80% were modified during the trial to reflect actual data not assumed data, which provides increased confidence in the results. A randomised control trial is considered high quality evidence, and this was a blinded RCT so no members of the trial knew if they were on the placebo or the treatment arm, thus responses are controlled for confounders. The trial was short term, at 4 months which reflects the speed at which the treatment benefits are achieved. However, longer term effects could not be studied. This was a small but well conducted RCT that shows clear evidence of significant benefit in reducing overall number of attacks, improving QoL, reducing site specific attacks in joints.
significance for anakinra Vs placebo for site specific attacks in: • joints • chest and abdomen	Ben-Zvi et al (2017)	9	Direct	Grade A	This outcome measure analysed site specific attacks of inflammation in the joints, chest, and abdomen. The best study for this outcome measure is identified as a double bind randomised control trial by Ben-Zvi et al (2017), although this is a small study the results are of high quality. The results analysed mean number attacks in the treatment arm compared to the placebo. The trial compared site attacks, and reported on the comparison and significance of attacks in joints, and in the chest and abdomen between anakinra Vs placebo and reported as follows: • A significant different in the number of site attacks in joints: P=0.019 (CI 0.8 +/- 1.6 Vs 2.1 +/- 1.1) • not a significant difference in site attacks in the chest p=0.3 • not a significant difference in site attacks in the abdomen p= 0.38 There appears to be evidence of significant reduction in joint attacks, however the significance was not high (acceptable range p<0.05) for attack rates in chest and abdomen. There are some uncertainties regarding this since the numbers involved start to be much smaller than considering overall attack rate. This was a small but well conducted RCT that shows clear evidence of significant benefit in reducing overall number of attacks, improving QoL, reducing site specific attacks in joints. The trial had a consistent dosing regimen for all participants, it is not clear whether an increased dose in partial responders may have

8.1 Use of Anakinra to treat cr-FMF compared to placebo					
					effected an increased response
significance for anakinra Vs placebo for CRP / SAA levels	Ben-Zvi et al (2017)	9	Direct	Grade A	This outcome measure considered CRP and SAA levels which are identified by laboratory analyses, unlike subjective markers they can provide a fairly objective assessment of which may or may not completely tally with the clinical symptoms. The best study for this outcome measure is identified as a double bind randomised control trial by Ben-Zvi et al (2017), although this is a small study the results are of high quality. • CRP and SAA levels were better in the anakinra treatment arm than in the placebo arm at p=0.069 however although this is an improvement it just falls short of the stated significance for p=<0.05 There are some uncertainties of this the trial was short term, at 4 months, which reflects the speed at which the immediate treatment benefits are achieved, but longer term effects were not studied. All participants received the same doses, and the study suggests that, based on previous experience with anakinra, a dose escalation may have been beneficial in unresponsive patients
significance for anakinra Vs placebo for quality of life (QOL) (visual analogue score)	Ben-Zvi et al (2017)	9	Direct	Grade A	This outcome measure assessed quality of life, using the Visual Analogue Score The best study for this outcome measure is identified as a double bind randomised control trial by Ben-Zvi et al (2017), although this is a small study the results are of high quality. Each trial arm undertook QOL tests and the results are significant for the treatment arm as follows: • Significance for anakinra Vs Placebo for Quality of Life (visual analogue score) p=0.045 (CI 7.7 +/- 2.3 Vs 4.2 +/- 2.9) There is clear evidence of improved quality of life to patients receiving anakinra for cr-FMF The uncertainties of this result are minimal. Although the sample size was fairly small, the assumptions used to calculate the sample size to a power of 80% were modified during the trial to reflect actual data not assumed data, which provides increased confidence in the results. A randomised control trial is considered high quality evidence, and this was a blinded RCT so no members of the trial knew if they were on the placebo or the treatment arm, thus responses are controlled for confounders. The trial was short term, at 4 months which reflects the speed at which the treatment benefits are achieved. However, longer term effects could not be studied. This was a small but well conducted RCT that shows clear evidence of significant benefit in reducing overall number of attacks, improving QoL, reducing site specific attacks in joints.
Adverse events	Ben-Zvi et al (2017)	9	Direct	Grade A	Adverse events could include method of administration or response to the drug. Ben-Zvi et al (2017), did not record very detailed adverse events in this paper, but noted that there were injection site reactions across the board, and that this was thought due to the vehicle of drug administration (subcutaneous injection) not the drug. The study stated that: • 2 people in the placebo arm discontinued due to AE. • 5 people in the placebo group discontinued due to treatment failure This provides us with a sense of the adverse events being related to the administration and this this becomes less tolerated if not in conjunction with a positive effect of treatment on the condition. The uncertainties of this result are minimal: the administration of placebo and treatment were the same so any adverse events from injection site reactions could be seen as such and not as a response to treatment toxicity.

8.1 Use of Anakinra to treat cr-FMF compared to placebo					
					This was a small but well conducted RCT that shows clear evidence of significant benefit in reducing overall number of attacks, improving QoL, reducing site specific attacks in joints.

8.2 Use of Anakinra to treat cr-FMF					
Outcome Measure	Reference	Quality of Evidence Score)	Applicability	Grade of Evidence	Interpretation of Evidence
Overall response of complete or partial remission	Van der Hilst (2016)	7	Direct	Grade A	All studies used a minimum of complete response, no response, or somewhere between the two: a partial response. Response was measured using both clinical and laboratory markers. Clinical markers included symptoms and number of attacks with complete response measuring no attacks, and partial response being a reduced frequency of attack. Laboratory markers (also reported as 'biochemical control') measure SAA and CRP levels: inflammation makers. Partial response includes complete remission of symptoms, but with elevated laboratory markers, or a reduction in symptoms and clear laboratory markers. V**an der Hilst et al (2016**) provide detail on the greatest number of cases by means of a clearly defined systematic review in which colchicine resistant FMF was treated with biologics, including anakinra. The results showed that of 64 patients treated with anakinra: • 95% of patients achieved a complete or partial response. The magnitude of a combined complete or partial response is consistent across the studies and is considerable. The uncertainties of evidence, which could impact on the extent of overall response include a lack of information regarding the dose-response relationship. It is not clear if an escalated dose would increase the non responders to a partial response. Other limitations of this evidence include that it is a review of published data because failure to respond is less likely to be written up as a successful case review for publication. However the extent of single case studies included in the evidence review was great, and the level of complete and partial response reported cannot be ignored. Where FMF is resistant to or where treatment is not tolerated with colchicine, it appears that anakinra provides a significant alternative treatment.
	Ozen et al (2017)	5	Direct		
	Ter Haar et al (2013	6	Direct		
	Rossi-Semerano et al (2015	6	Direct		
	Basaran et al (2014)	6	Direct		
Complete response -	Van der Hilst (2016)	7	Direct	Grade A	All studies used a minimum of complete response, no response, or somewhere between the two: a partial response. Complete response was measured using both clinical and laboratory markers. Clinical markers included symptoms and number of attacks with complete response measuring no attacks, laboratory markers (also reported as 'biochemical control') measure SAA and CRP levels: inflammation makers. V**an der Hilst et al (2016**) provide detail on the greatest number of cases by means of a clearly defined systematic review in which colchicine resistant FMF was treated with biologics, including anakinra. The results showed that of 64 patients treated with anakinra: • 76.5% achieved a complete response, The magnitude of a complete response is consistent across the studies and is considerable.
	Ozen et al (2017)	5	Direct		
	Ter Haar et al (2013	6	Direct		
	Rossi-Semerano et al (2015	6	Direct		
	Basaran et al (2014)	6	Direct		

8.2 Use of Anakinra to treat cr-FMF					
					The uncertainties of evidence, which could impact on the extent of overall response include a lack of information regarding the dose-response relationship. It is not clear if an escalated dose would increase the partial responders into the complete response outcome. Other limitations of this evidence include that it is a review of published data because failure to respond is less likely to be written up as a successful case review for publication. However the extent of single case studies included in the evidence review was great, and the level of complete response reported cannot be ignored. Where FMF is resistant to or where treatment is not tolerated with colchicine, it appears that anakinra provides a significant alternative treatment.
Partial response	Van der Hilst (2016)	7	Direct	Grade A	All studies used a minimum of complete response, no response, or somewhere between the two: a partial response. Response was measured using both clinical and laboratory markers. Clinical markers included symptoms and number of attacks. Laboratory markers (also reported as 'biochemical control') measure SAA and CRP levels: inflammation makers. Partial response includes complete remission of symptoms, but with elevated laboratory markers, or a reduction in symptoms and clear laboratory markers. V**an der Hilst et al (2016**) provide detail on the greatest number of cases by means of a clearly defined systematic review in which colchicine resistant FMF was treated with biologics, including anakinra. The results showed that of 64 patients treated with anakinra: • 18.8% decrease in attack frequency (a partial response to treatment) The magnitude of a partial response is consistent across the studies and is limited in proportion by the overwhelmingly high proportion of people showing a complete response. The uncertainties of evidence include a lack of information regarding the dose-response relationship. It is not clear if an escalated dose would increase the non responders to a partial response. Other limitations of this evidence include that it is a review of published data because failure to respond is less likely to be written up as a successful case review for publication. However the extent of single case studies included in the evidence review was great, and the level of complete and partial response reported cannot be ignored. Where FMF is resistant to or where treatment is not tolerated with colchicine, it appears that anakinra provides a significant alternative treatment.
	Ozen et al (2017)	5	Direct		
	Ter Haar et al (2013	6	Direct		
	Rossi-Semerano et al (2015	6	Direct		
	Basaran et al (2014)	6	Direct		
No response	Van der Hilst (2016)	7	Direct	Grade A	All studies used a minimum of complete response, no response, or somewhere between the two: a partial response. Response was measured using both clinical and laboratory markers. Clinical markers included symptoms and number of attacks with complete response measuring no attacks, and partial response being a reduced frequency of attack. Laboratory markers (also reported as 'biochemical control') measure SAA and CRP levels: inflammation makers. Partial response includes complete remission of symptoms, but with elevated laboratory markers, or a reduction in symptoms and clear laboratory markers. V**an der Hilst et al (2016**) provide detail on the greatest number of cases by means of a clearly defined systematic review in which
	Ozen et al (2017)	5	Direct		
	Ter Haar et al (2013	6	Direct		
	Rossi-Semerano et al (2015	6	Direct		

8.2 Use of Anakinra to treat cr-FMF					
	Basaran et al (2014)	6	Direct		colchicine resistant FMF was treated with biologics, including anakinra. The results showed that of 64 patients treated with anakinra • 3 failed to respond The magnitude of a combined complete or partial response is consistent across the studies and is considerable, what this suggests is that if patients are going to respond then they will clearly do so by the markers used. The uncertainties of evidence, which could impact on the extent of overall response include a lack of information regarding the dose-response relationship. It is not clear if an escalated dose would increase the non responders to a partial response. There are some limitations with reviewing published data because failure to respond is less likely to be written up as a successful case review for publication, and thus might bias the results. However the number of single case studies included in the evidence review was great, and consistent with the prospective cohort study reported by Basaran et al (2015) The low level of non-response suggests that there is compelling evidence to support the use of anakinra in treating FMF where the usual treatment of colchicine is not tolerated or ineffective.
Observations on type AA Amyloidosis in 19 patients	Van der Hilst (2016)	7	Direct	Grade A	AA Amyloidosis is a condition that is linked to periodic inflammatory fever and the chronic nature of this condition. V**an der Hilst et al (2016**) identified a number of cases in their systematic review in which colchicine resistant FMF was treated with anakinra. They reported on observations on type AA Amyloidosis in 19 patients. Their observations show: • 4 pts had nephrotic syndrome, which showed a decrease in proteinuria after anakinra started. • 5 pts had anakinra post renal transplant and showed no recurrence of AA amyloidosis. • 8 pts had end stage renal disease 3 of which had transplantation on anakinra with no recurrence of amyloidosis. Although these are only secondary outcomes and observations, and the observations should be treated with caution, they show that anakinra may benefit patients undergoing transplant, since use of anakinra appears to reduce the recurrence of amyloidosis following transplant. The limitations of this outcome are high in that these were secondary outcomes noted as an observation.

8.2 Use of Anakinra to treat cr-FMF					
Associated treatment reduction (ATR)	Rossi-Semerano et al (2015)	6	Direct	Grade A	Associated treatment reduction (ATR) is a benefit to an effective treatment. Periodic inflammatory conditions are currently treated with a range of medications designed to reduce fever, aches, and the many and varying symptoms of the condition. These medications (high dose steroids, NSAIDS etc) have effects of their own from long term use or high dose, as such understanding the reduction of these associated treatments can help assess additional benefits of the treatment. This outcome looks at the reduction in associated treatment in effective use of anakinra. Rossi Semerano et al (2015) undertook the most comprehensive assessment of ATR in their nationwide survey of off-label IL-1 treatments, by evaluating physician questionnaires. Data collected included information on other medications used in the management of disease. 8 patients with FMF continued to receive colchicine with anakinra, but the data also showed that 6 of 9 cases were able to reduce their associated treatments. The impact of reducing associated treatments could be of considerable benefit to patients. The data presented are confusing and incomplete but could suggest that other treatments used to moderate signs and symptoms of FMF can be reduced successfully as a result of anakinra use.
Adverse events	Rossi-Semerano et al (2015)	6	Direct	Grade A	Adverse events include impact from the method of administration (sub cutaneous injection) and the impact of the medication itself. Very few papers provided significant detail on adverse events although they all mentioned injection site reactions to some degree or other. However Rossi-Semerano et al (2015) undertook a detailed assessment of adverse events in their retrospective analysis of patients following data request from physician. Rossi-Semerano et al (2015) is reflected here as the best study reporting outcomes of adverse events: they evaluated the use of anakinra in 185 patients, most with daily injections (a few on demand). They detailed the safety and adverse events relating to the use of anakinra as a whole not by disease. Adults received 100 mg, children 1-6mg/kg/day, 8 patients with FMF received colchicine with anakinra Rossi-Semerano et al (2015) outcomes showed: • minor injection site reactions 39%, which were more frequent in children than adults, 90.2% (CI 77.5-96.1) vs 48% (2 39.9-56.5) p=<0.0001 • injection site pain 36% • liver enzymes elevation 7% • weight increase 11% • respiratory infections 2.8% • severe infection 9% • liver toxicity although rare overall, was more frequent in children than adults which appeared to be associated with treatment duration: 17% (CI 8.5-31.3) vs 4.4% (2.0-9.4) p=<0.05 The results of these evaluations suggest that the most common adverse event is injection site reaction or pain which was identified in a significant proportion of patients. Other adverse events which are experienced less frequently could be considered to be greater concern, especially where the frequency is greater in children. For example liver toxicity, although a rare side effect, is more common in children. The authors suggest that this may be due to longer term use, but this is not clear. The limitations of these results are in that they apply to treatment by anakinra, not specific to condition, although it is reasonable to extrapolate these data to condition.
	Van der Hilst (2016)	7	Direct		
	Basaran et al (2014)	6	Direct		

8.3 Use of Anakinra to treat TRAPS					
Outcome Measure	Reference	Quality of Evidence Score)	Applicability	Grade of Evidence	Interpretation of Evidence
Complete response to treatment	Gattorno et al (2008)	7	Direct	A	Complete response to treatment for TRAPS patients was measured by evaluating the patients' global assessment of disease activity, number and duration of episodes, symptoms and levels of C-reactive protein (CRP) and SAA. Gattorno M, et al (2008) presented a prospective cohort study of five patients with poorly controlled TRAPS requiring high dose steroids. Of the five, three patients had prolonged and frequent attacks, and two patients had chronic disease. The cohort was given daily treatment with anakinra daily: 1.5mg/kg/day, and monitored. This was a small study but as a prospective cohort design provides a higher quality study than retrospective evaluations. Gattorno et al (2008) reported a complete response of: • 100% (n=5) of patients at follow up (mean 11.4 mths, range 4-20 mths), showed no episodes of disease, and normal levels of SAA. This study is particularly useful as the treatment was stopped and then started again, with disease control reported. After 2 days of treatment, (starting at a new episode of disease) all 5 showed disappearance of fever and other clinical manifestations. 4 paediatric patients stopped anakinra after 15 days and all relapsed at between 3-8 days. Re-introduction resulted in prompt improvement. This was the most authentic study as Gattorno et al reported on the outcomes of a prospective cohort of patients, whereas other research evaluated retrospective information supplied by physicians. However the cohort is very small, with only 5 people which presents limitations to the information we can extrapolate. The results should be viewed with caution as they are small numbers, and did not provide any detailed information on a range of mutations found in TRAPS. Ozen et al (2017) and Ter Haar et al (2013) suggest that the TRAPS mutation R92Q responds less well to anakinra than other TRAPS mutations, and this should be considered (and would be picked up in the prescribing criteria).
	Ter Haar et al (2013)	6	Direct		
	Ozen et al (2017)	5	Direct		
	Rossi-Semerano et al (2015)	6	Direct		
Partial response to treatment	Gattorno et al (2008)	7	Direct	A	A response to treatment was measured by evaluating the patients' global assessment of disease activity, number and duration of episodes, symptoms and levels of C-reactive protein (CRP) and SAA. Gattorno M, et al (2008) presented a prospective cohort study of five patients with poorly controlled TRAPS requiring high dose steroids. Of the five, three patients had prolonged and frequent attacks, and two patients had chronic disease. The cohort was given daily treatment with anakinra daily: 1.5mg/kg/day, and monitored. This was a small study but as a prospective cohort design provides a higher quality study than retrospective evaluations. Gattorno et al (2008) reported that all patients had a complete response at follow up, thus no partial response was recorded. This was the most authentic study as Gattorno et al reported on the outcomes of a prospective cohort of patients, whereas other research evaluated retrospective information supplied by physicians, or evaluated case studies. However the cohort is very small, with only 5 people which presents limitations to the information we can extrapolate. The results did not provide information on a range of mutations found in TRAPS. Ozen et al (2017) and Ter Haar et al (2013) suggest that the TRAPS mutation R92Q responds less well to anakinra than other TRAPS mutations, and this should be considered (and would be picked up in the prescribing
	Ter Haar et al (2013)	6	Direct		
	Ozen et al (2017)	5	Direct		
	Rossi-Semerano et al (2015	6	Direct		

					criteria).
Serum levels of C-reactive protein (CRP) and SAA in the normal range	Gattorno et al (2008) Ter Haar et al (2013) Ozen et al (2017) Rossi-Semerano et al (2015)	7 6 5 6	Direct Direct Direct Direct	A	Serum levels provide an objective measure of response to treatment. Gattorno M, et al (2008) presented a prospective cohort study of five patients with poorly controlled TRAPS requiring high dose steroids. Of the five, three patients had prolonged and frequent attacks, and two patients had chronic disease. The cohort was given daily treatment with anakinra daily: 1.5mg/kg/day, and monitored. This was a small study but as a prospective cohort design provides a higher quality study than retrospective evaluations. • 100% (n=5) of patients at follow up (mean 11.4 mths, range 4-20 mths), showed normal levels of SAA. The results should be viewed with caution as they are small numbers, and did not provide information on a range of mutations found in TRAPS. Ozen et al (2017) and Ter Haar et al (2013) suggest that the TRAPS mutation R92Q responds less well to anakinra than other TRAPS mutations, and this should be considered (and would be picked up in the prescribing criteria). This was the most authentic study as Gattorno et al reported on the outcomes of a prospective cohort of patients, whereas other research evaluated retrospective information supplied by physicians. The data are broadly consistent with other studies. The results did not provide information on a range of mutations found in TRAPS. Ozen et al (2017) and Ter Haar et al (2013) suggest that the TRAPS mutation R92Q responds less well to anakinra than other TRAPS mutations, and this should be considered (and would be picked up in the prescribing criteria).
Reduction in associated treatment	Gattorno et al (2008) Ter Haar et al (2013) Ozen et al (2017 Rossi-Semerano et al (2015	7 6 5 6	Direct Direct Direct Direct	A	Associated treatment reduction (ATR) is a benefit identified with the introduction of an effective main treatment. Periodic inflammatory conditions are currently treated with a range of medications designed to reduce fever, aches, and the many and varying symptoms of the condition. These medications (high dose steroids, NSAIDS etc) have effects of their own from long term use or high dose, as such understanding the reduction of these associated treatments can help assess additional benefits of the treatment. This outcome looks at the reduction in associated treatment in effective use of anakinra. Gattorno et al (2008) presented a prospective cohort study of five patients with poorly controlled TRAPS requiring high dose steroids. Of the five, three patients had prolonged and frequent attacks, and two patients had chronic disease. The cohort was given daily treatment with anakinra daily: 1.5mg/kg/day. This was the most authentic study as Gattorno et al (2008) reported on the outcomes of a prospective cohort of patients, whereas other research evaluated retrospective information supplied by physicians. • 100% (n=5) of patients at follow up (mean 11.4 mths, range 4-20 mths), had been able to reduce associated treatments. • 4 patients no longer required steroid therapy and one patient reduced steroid treatment to maintain other respiratory symptoms. The clinical benefit to patients in reducing associated treatments with negative long term effects is great. However there are limitations to this study due to the small numbers, however the data are broadly consistent with other studies. The results did not provide information on a range of mutations found in TRAPS. Ozen et al (2017) and Ter Haar et al (2013) suggest that the TRAPS mutation R92Q responds less well to anakinra than other TRAPS mutations, and this should be considered (and would be picked up in the prescribing criteria), and have an associated impact in the opportunity to reduce other treatments

Adverse events	Gattorno et al (2008)	7	Direct	A	Adverse events could include method of administration or response to the drug. Most publications provided a cursory assessment of adverse events although usually noted that injection site reactions were common. Gattorno M, et al (2008) presented a prospective cohort study of five patients with poorly controlled TRAPS requiring high dose steroids. Of the five, three patients had prolonged and frequent attacks, and two patients had chronic disease. The cohort was given daily treatment with anakinra daily: 1.5mg/kg/day • 100% of patients in this cohort had a reaction at the site of injection • 0% had any serious adverse events. This provides us with a sense of the adverse events being related to the administration rather than medication issues. This lends itself to the consideration of the balance between administration effects and severity of disease. The limitations are considerable since this is a small study, however table 8.2i provides more detail about the safety of anakinra overall, and not just with regards to treatment for TRAPS.
	Ter Haar, N. et al (2013)	6	Direct		
	Ozen S et al (2017)	5	Direct		
	Rossi-Semerano, L. et al (2015)	6	Direct		

8.4 Use of anakinra to treat HIDS / MKD					
Outcome Measure	Reference	Quality of Evidence Score)	Applicability	Grade of Evidence	Interpretation of Evidence
Overall response to treatment: a complete or partial response	Ozen et al (2017)	5	Direct	B	Overall response to treatment includes the following responses: • complete response: resolution of inflammatory attacks; • partial response, improvement of symptoms during inflammatory attacks, and • positive response, reported as effective but with limited available detail. Kostjukovits. et al (2015) undertook a systematic review of 33 published case reports on paediatric HIDS patients treated with biological medicine. Of these 21 were treated with Anakinra. This provides the best study for these outcomes • 90% of cases (n=19) treated with anakinra showed an overall complete, partial or positive response This indicates a significant clinical benefit to patients. The limitations of the research are inherent in a systematic review of available literature, with some potential for publication bias and variation in clinical management as data were collated from a number of centres. However, this is one of very few reviews for this condition and treatment. As far as this review goes, there appears to be good outcomes from using biologics including anakinra Eligibility was based on <18 years old, with biologic treatment and genetically confirmed HIDS. Cases were cross referenced to exclude duplicates. Patients received continuous treatment with varying doses in all but 4 people who dosed on demand.
	Ter Haar et al (2013)	6	Direct		
	Rossi-Semerano et al (2015)	6	Direct		
	Kostjukovits et al (2015	5	Direct		
Complete response to treatment	Ozen et al (2017)	5	Direct	B	This outcome measure reported complete response to anakinra as total resolution of inflammatory attacks. Kostjukovits et al (2015) undertook a systematic review of 33 published case reports on paediatric HIDS patients treated with biological medicine. Of these 21 were treated with Anakinra. This provides the best study for these outcomes 19% of cases (n=4) treated with anakinra showed a complete response. The limitations of the research are inherent in a systematic review of available literature, with some potential for publication bias: only those published cases were included in the review, and cases are more likely to be published if positive. In addition variation in clinical management and disease interpretation may be present, as data were collated from a number of centres. However, this is one of very few reviews for this condition and treatment. As far as this review goes, there appears to be good outcomes from using biologics including anakinra Eligibility was based on <18 years old, with biologic treatment and genetically confirmed HIDS. Cases were cross referenced to exclude duplicates. Patients received continuous treatment with varying doses in all but 4 people who dosed on demand.
	Ter Haar et al (2013)	6			
	Rossi-Semerano et al (2015)	6			
	Kostjukovits et al (2015	5			
Partial response to treatment	Ozen et al (2017)	5	Direct	B	This outcome measure reported a partial response to anakinra as an improvement of symptoms during inflammatory attacks. Kostjukovits et al (2015) undertook a systematic review of 33 published case reports on paediatric HIDS patients treated with biological medicine. Of these 21 were treated with Anakinra. This provides the best study for these outcomes • 71% of cases (n=15) treated with anakinra showed a partial response. This is a significant response, and indicates a high clinical benefit to patients.
	Ter Haar et al (2013)	6			
	Rossi-Semerano et al (2015)	6			
	Kostjukovits et al (2015	5			

8.4 Use of anakinra to treat HIDS / MKD					
					The limitations of the research are inherent in a systematic review of available literature, with some potential for publication bias: only those published cases were included in the review, and cases are more likely to be published if positive. In addition variation in clinical management and disease interpretation may be present, as data were collated from a number of centres. However, this is one of very few reviews for this condition and treatment. As far as this review goes, there appears to be good outcomes from using biologics including anakinra Eligibility was based on <18 years old, with biologic treatment and genetically confirmed HIDS. Cases were cross referenced to exclude duplicates. Patients received continuous treatment with varying doses in all but 4 people who dosed on demand.
No change to treatment	Ozen et al (2017)	5	Direct	B	This outcome measure reported no response to treatment Kostjukovits et al (2015) undertook a systematic review of 33 published case reports on paediatric HIDS patients treated with biological medicine. Of these 21 were treated with Anakinra. Eligibility was based on <18 years old, with biologic treatment and genetically confirmed HIDS. Cases were cross referenced to exclude duplicates. Patients received continuous treatment with varying doses in all but 4 people who dosed on demand. This provides the best study for these outcomes • 5% of cases (n=1) treated with anakinra showed no response This is a significant response, and indicates that no response is rare and that anakinra may be of use in poorly controlled HIDS / MKD. The limitations of the research are inherent in a systematic review of available literature, with some potential for publication bias: only those published cases were included in the review, and cases are more likely to be published if positive. In addition variation in clinical management and disease interpretation may be present, as data were collated from a number of centres. However, this is one of very few reviews for this condition and treatment. As far as this review goes, there appears to be good outcomes from using biologics including anakinra.
	Ter Haar et al (2013)	6			
	Rossi-Semerano et al (2015)	6			
	Kostjukovits et al (2015	5			
Worsening response to treatment	Ozen et al (2017)	5	Direct	B	This outcome measure reported cases where treatment appeared to worsen the condition. Kostjukovits et al (2015) undertook a systematic review of 33 published case reports on paediatric HIDS patients treated with biological medicine. Of these 21 were treated with Anakinra. Eligibility was based on <18 years old, with biologic treatment and genetically confirmed HIDS. Cases were cross referenced to exclude duplicates. Patients received continuous treatment with varying doses in all but 4 people who dosed on demand. This provides the best study for these outcomes • 5% of cases (n=1) treated with anakinra showed a worsening in response to treatment This is a significant response, and indicates that a worsening condition, as in a non-responding condition is rare and that anakinra may be of use in poorly controlled HIDS / MKD. The limitations of the research are inherent in a systematic review of available literature, with some potential for publication bias: only those published cases were included in the review, and cases are more likely to be published if positive. In addition variation in clinical management and disease interpretation may be present, as data were collated from a number of centres. However, this is one of very few reviews for this condition and treatment. As far as this review goes, there appears to be good outcomes from using biologics including anakinra.
	Ter Haar et al (2013)	6			
	Rossi-Semerano et al (2015)	6			
	Kostjukovits et al (2015	5			

<table>
<tr><th colspan="6">8.4 Use of anakinra to treat HIDS / MKD</th></tr>
<tr><td rowspan="4">Adverse events</td><td>Ozen et al (2017)</td><td>5</td><td>Direct</td><td rowspan="4">B</td><td rowspan="4">Adverse events include impact from the method of administration (sub cutaneous injection) and the impact of the medication itself.

Very few papers provided significant detail on adverse events although they all mentioned injection site reactions to some degree or other. However Rossi-Semerano et al (2015) undertook a detailed assessment of adverse events in their retrospective analysis of patients following data request from physician.

Rossi-Semerano et al (2015) is reflected here as the best study reporting outcomes of adverse events: they evaluated the use of anakinra in 185 patients, most with daily injections (a few on demand). They detailed the safety and adverse events relating to the use of anakinra as a whole not by disease. Adults received 100 mg, children 1-6mg/kg/day, 8 patients with FMF received colchicine with anakinra

Rossi-Semerano et al (2015) outcomes showed:

• minor injection site reactions 39%, which were more frequent in children than adults, 90.2% (CI 77.5-96.1) vs 48% (2 39.9-56.5) p=<0.0001
• injection site pain 36%
• liver enzymes elevation 7%
• weight increase 11%
• respiratory infections 2.8%
• severe infection 9%
• liver toxicity although rare overall, was more frequent in children than adults which appeared to be associated with treatment duration: 17% (CI 8.5-31.3) vs 4.4% (2.0-9.4) p=<0.05

The results of these evaluations suggest that the most common adverse event is injection site reaction or pain which was identified in a significant proportion of patients. Other adverse events which are experienced less frequently could be considered to be greater concern, especially where the frequency is greater in children. For example liver toxicity, although a rare side effect, is more common in children. The authors suggest that this may be due to longer term use, but this is not clear. The limitations of these results are in that they apply to treatment by anakinra, not specific to condition, although it is reasonable to extrapolate these data to condition.</td></tr>
<tr><td>Ter Haar et al (2013)</td><td>6</td><td></td></tr>
<tr><td>Rossi-Semerano et al (2015)</td><td>6</td><td></td></tr>
<tr><td>Kostjukovits et al (2015</td><td>5</td><td></td></tr>
</table>

8.5 Use of anakinra to treat Schnitzler's syndrome					
Outcome Measure	Reference	Quality of Evidence Score)	Applicability	Grade of Evidence	Interpretation of Evidence
Overall benefit of greater than 50% improvement	Neel, A et al (2014)	6	Direct	B	Overall benefit to treatment was measured as patients with complete or partial remission as measured by signs and symptoms and laboratory markers. Neel et al (2014) undertook a retrospective analysis of efficacy of treatment outcomes 29 patients were treated with anakinra, 24 of which had previously failed immunomodulating, immunosuppressive, or non anti-IL-1 treatment. • All patients had complete or partial remission at last follow up (median 6 mths, range 3-79 mths) The mean age of patients using anakinra was relatively elderly at 65.9 (+/-10.7 yrs.) so it is difficult to generalise outcomes to all ages. However, it seems likely that if all patients in this cohort benefited, then so would other patients. The usual limitations of inherent bias in retrospective studies apply here, e.g.: recollection difficulties, choice of studies to include, which cases were written up, as these elements will influence the availability of studies for review. In addition, only patients with a very severe condition were included since other patients are sent to dermatologists and were not thus included in the denominator of this study. However, this paper was the largest analysis of efficacy of anakinra in patients with Schnitzler's syndrome, and the clinical benefit to the patient group is significant. The paper concludes that response to anakinra is so immediate and considerable that anakinra could be considered diagnostic in this case of periodic fever. That is: if 'no response' then one might need to reconsider a diagnosis of Schnitzler's syndrome.
	Rossi-Semerano, L. et al (2015	6	Direct		
Complete remission	Neel et al (2014)	6	Direct	B	Complete remission following treatment was identified where signs and symptoms and laboratory markers were all considered normal. Neel et al (2014) undertook a retrospective analysis of efficacy of treatment outcomes 29 patients were treated with anakinra, 24 of which had previously failed immunomodulating, immunosuppressive, or non anti-IL-1 treatment, and this provides the best study for this analysis. • 24 of 29 patients receiving anakinra were in complete remission at last follow up. • 3 had mild residual bone pain It is worth noting that only 4 achieved complete remission with spaced injections, daily injections had to be resumed for the others. The mean age of patients using anakinra was relatively elderly at 65.9 (+/-10.7 yrs.) so it is difficult to generalise outcomes to all ages. However, it seems likely that if all patients in this cohort benefited, then so would other patients. The usual limitations of inherent bias in retrospective studies apply here, e.g.: recollection difficulties, choice of studies to include, which cases were written up, as these elements will influence the availability of studies for review. In addition, only patients with a very severe condition were included since other patients are sent to dermatologists and were not thus included in the denominator of this study.
	Rossi-Semerano et al (2015)	6	Direct		

8.5 Use of anakinra to treat Schnitzler's syndrome					
					However, this paper was the largest analysis of efficacy of anakinra in patients with Schnitzler's syndrome, and the clinical benefit to the patient group is significant. The paper concludes that response to anakinra is so immediate and considerable that anakinra could be considered diagnostic in this case of periodic fever. That is: if 'no response' then one might need to reconsider a diagnosis of Schnitzler's syndrome.
Partial remission	Neel et al (2014)	6	Direct	B	Partial remission was identified where signs and symptoms and laboratory markers may not all be considered normal. It is worth noting that of the five patients in partial remission three were asymptomatic and with normal CRP levels, and two had intermittent skin rash and pain. Neel et al (2014) undertook a retrospective analysis of efficacy of treatment outcomes 29 patients were treated with anakinra, 24 of which had previously failed immunomodulating, immunosuppressive, or non anti-IL-1 treatment. This best study identified that: • 5 of 29 patients receiving anakinra were in partial remission at last follow up. The mean age of patients using anakinra was relatively elderly at 65.9 (+/-10.7 yrs.) so it is difficult to generalise outcomes to all ages. However, it seems likely that if all patients in this cohort benefited, then so would other patients. The usual limitations of inherent bias in retrospective studies apply here, e.g.: recollection difficulties, choice of studies to include, which cases were written up, as these elements will influence the availability of studies for review. In addition, only patients with a very severe condition were included since other patients are sent to dermatologists and were not thus included in the denominator of this study. However, this paper was the largest analysis of efficacy of anakinra in patients with Schnitzler's syndrome, and the clinical benefit to the patient group is significant. The paper concludes that response to anakinra is so immediate and considerable that anakinra could be considered diagnostic in this case of periodic fever. That is: if 'no response' then one might need to reconsider a diagnosis of Schnitzler's syndrome.
	Rossi-Semerano et al (2015)	6	Direct		
Time To Treatment effect (TTT)	Neel et al (2014)	6	Direct	B	Neel et al (2014) undertook a retrospective analysis of efficacy of treatment outcomes for 29 patients treated with anakinra. This study was comprehensive in reporting outcomes to treatment including to treatment effect for starting anakinra. Neel et al (2014) reported that: • All 29 patients receiving anakinra experienced improvement within 48 hrs of starting IL-1Ra. This is consistent with other reported experiences of anakinra treatment: when it works it works quickly. The mean age of patients using anakinra was relatively elderly at 65.9 (+/-10.7 yrs.) so it is difficult to generalise to all ages. The usual limitations of inherent bias in retrospective studies apply here, e.g.: recollection difficulties, choice of studies to include, which cases were written up etc. In addition, only patients with a very severe condition were included since other patients are sent to dermatologists and were not thus included in the denominator of this study. However the results present a very compelling indication of speed of treatment effect.
	Rossi-Semerano et al (2015)	6	Direct		

8.5 Use of anakinra to treat Schnitzler's syndrome					
					The paper concludes that response to anakinra is so immediate and considerable that anakinra could be considered diagnostic in this case of periodic fever.
Discontinuation of concomitant therapy	Neel et al (2014)	6	Direct	B	Discontinuation of concomitant therapy (also reported in other studies as ATR) is a benefit identified with the introduction of an effective main treatment. Periodic inflammatory conditions are currently treated with a range of medications designed to reduce fever, aches, and the many and varying symptoms of the condition. These medications (high dose steroids, NSAIDS etc) have negative side effects of their own from long term use or high dose, as such understanding the reduction of these associated treatments can help assess additional benefits of the treatment. This outcome looks at the reduction in associated treatment in effective use of anakinra. Neel et al (2014) undertook a retrospective analysis of efficacy of treatment outcomes for 29 patients treated with anakinra. • 26 of 29 patients discontinued concomitant therapies • 3 patients stayed on low dose corticosteroids for residual symptoms. The magnitude of impact and resulting discontinuation of other therapies is of note. There are clearly significant benefits associated with anakinra treatment in this condition. Notwithstanding the usual limitations of inherent bias in retrospective studies e.g.: recollection difficulties, choice of studies to include, which cases were written up etc. and that only patients with a very severe condition were included, the clinical benefit to the patient group of ATR is significant.
	Rossi-Semerano et al (2015)	6	Direct		
Adverse events	Neel et al (2014)	6	Direct	B	Adverse events could include method of administration or response to the drug. Neel et al (2014) undertook a retrospective analysis of efficacy of treatment outcomes for 42 patients who were treated with IL-1 blockers, and those not treated with IL-1 Blockers. Of the 29 patients treated with anakinra, 24 had failed immunomodulating, immunosuppressive, or non anti-IL-1 treatment. Neel et al (2014) reported on adverse events in Schnitzler's syndrome patients taking anakinra as follows: • 5 patients had injection site reactions • 6 had severe infection (sore throat and 5 pneumonia. 4 of the patients developing pneumonia had predisposing factors of COPD) • 3 patients developed neutropenia (1 fine after adjusting dose, 1 by spacing injections and 1 cleared up after 3rd attempt) The study results broadly reflect other researchers' results on adverse events to anakinra use for other conditions, see also table 8.2i. That this study reflects condition specific patients is useful but does have limitations particular to this study. The mean age of patients using anakinra was relatively elderly at 65.9 (+/-10.7 yrs.) so it is difficult to generalise these results to all ages. It is also not clear the degree to which predisposing factors influenced adverse events or only a partial response. Dosing adjustments circumvented some
	Rossi-Semerano et al (2015)	6	Direct		

8.5 Use of anakinra to treat Schnitzler's syndrome					
					side effects, and one patient developed AA amyloidosis, IL1Ra led to complete remission, but no improvement to the proteinuria. The usual limitations of inherent bias in retrospective studies apply here, e.g.: recollection difficulties, choice of studies to include, which cases were written up etc. In addition, only patients with a very severe condition were included since other patients are sent to dermatologists and were not thus included in the denominator of this study.

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?	Adult and paediatric (2 years and above): • ***Colchicine resistant familial Mediterranean fever (crFMF):*** *Adult and paediatric (2 years and above) patients in whom colchicine is contraindicated, is not tolerated, or does not provide an adequate response despite the highest tolerable dose of colchicine* • ***Hyperimmunoglobulin D Syndrome (HIDS)/Mevalonate Kinase Deficiency (MKD):*** *Adult and paediatric (2 years and above) patients* • ***Tumour necrosis factor receptor–associated periodic syndrome (TRAPS):*** *Adult and paediatric (2 years and above) patients* • ***Schnitzler's syndrome:*** *Adult and paediatric (2 years and above) patients* • ***Undifferentiated periodic fever and auto inflammatory disease***
I – Intervention Which intervention, treatment or approach should be used?	Anakinra
C – Comparison What is/are the main alternative/s to compare with the intervention being considered?	Best usual care Placebo control Colchicine (in cr-FMF)
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 Prevention of disease flares Adverse treatment effects Quality of life Normalisation of laboratory measures of disease activity to inform on risk of amyloidosis (serum amyloid A protein level (SAA)) *Important to decision-making:* Physician global assessment of disease activity (PGA) Subjective symptom scores Adherence to treatment
Assumptions / limits applied to search	

Inclusion Criteria	English language 1990-present (2-4) 2016-2017 (1) RCT, systematic review, prospective cohort studies, case-control studies.
Exclusion Criteria	Non-peer reviewed journal Discussion piece Conference abstract Small study size (<4 people) Retrospective case reviews (<100 cases)

10. Search Strategy

PHE libraries (Susan Rose and Barbara Norrey, Knowledge and Evidence Specialist, Knowledge and Library Services) were asked to run 5 literature search strategies to identify potential papers for review.

Search one, was undertaken on 24 March 2017, and the searches two to five (incl) were undertaken on 24 August 2016.

1	**Anakinra: KEYWORDS**	**Results MEDLINE**	**Results EMBASE**
1.	(colchicine).ti,ab	(13,926)	(16,830)
2.	*COLCHICINE/	(5,819)	(11,522)
3.	(colcrys OR mitigare).ti,ab	(5)	(14)
4.	(1 OR 2 OR 3)	(15,138)	(20,978)
5.	(resistan*).ti,ab	(805,587)	(1,010,776)
6.	(intoleran*).ti,ab	(33,230)	(50,096)
7.	(contra* indicat*).ti,ab	(231,725)	(5,364)
8.	(5 OR 6 OR 7)	(1,050,591)	(1,068,013
9.	(4 AND 8)	(1,688)	(2,957)
10	(familial mediterranean fever*).ti,ab	(2,778)	(4,033)
11	exp *"FAMILIAL MEDITERRANEAN FEVER"/	(2,848)	(3,645)
12	(FMF OR CRFMF OR crFMF).ti,ab	(1,940)	(3,174)
13	(colchicine*resistant FMF).ti,ab	(34)	(4)
14	(hyperimmunoglobulin D syndrome OR HIDS).ti,ab	(206)	(359)
15	(Mevalonate kinase deficiency OR MKD).ti,ab	(254)	(350)
16	(Mevalonate kinase associated periodic fever syndrome).ti,ab	(75)	(1)
17	(Tumo*r necrosis factor receptor*associated periodic syndrome* OR TRAPS).ti,ab	(13,693)	(14,302)
18	(Schnitzler syndrome).ti,ab	(216)	(174)
19	(cryopyrin associated periodic syndrome* OR CAPS).ti,ab	(7,640)	(9,658)
20	(periodic auto*inflammatory fever*).ti,ab	(385)	(1)
21	(TNF receptor*associated periodic syndrome*).ti,ab	(89)	(1)
22	(10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 2 1)	(25,519)	(29,612)
23	(anakinra).ti,ab	(1,190)	(2,364)
24	(kineret).ti,ab	(69)	(137)
25	(23 OR 24)	(1,211)	(2,974)
26	(9 AND 22 AND 25)	(32)	(82)
27	26 [DT 2016-2017]	(10)	16
Results Medline + EMBASE = 26 7 duplicates removed		**TOTAL RESULTS = 19**	

2 Search History – FMS	3 TRAPS:
1. Medline; colchicine.ti,ab; 13581 results. 2. Medline; exp COLCHICINE/; 14205 results. 3. Medline; (colcrys OR mitigare).ti,ab; 5 results. 4. Medline; 1 OR 2 OR 3; 19347 results. 5. Medline; resistan*.ti,ab; 759142 results. 6. Medline; intoleran*.ti,ab; 31261 results. 7. Medline; contraindicat*.ti,ab; 38097 results. 8. Medline; contra-indicat.ti,ab; 0 results. 9. Medline; 5 OR 6 OR 7; 821533 results. 10. Medline; 4 AND 9; 1546 results. 11. Medline; (familial AND mediterranean AND fever).ti,ab; 2614 results. 12. Medline; exp FAMILIAL MEDITERRANEAN FEVER/; 3138 results. 13. Medline; FMF.ti,ab; 1815 results. 14. Medline; 11 OR 12 OR 13; 4025 results. 15. Medline; 10 AND 14; 104 results. 16. Medline; crFMF.ti,ab; 0 results. 17. Medline; canakinumab.ti,ab; 236 results. 18. Medline; Ilaris.ti,ab; 14 results. 19. Medline; 17 OR 18; 238 results. 20. Medline; anakinra.ti,ab; 1076 results. 21. Medline; Kineret.ti,ab; 67 results. 22. Medline; 20 OR 21; 1096 results. 23. Medline; 19 OR 22; 1248 results. 24. Medline; 15 AND 23; 30 results. 25. EMBASE; 15 AND 23; 82 results. 26. CINAHL; 15 AND 23; 4 results. 27. Medline; 24 [Limit to: Publication Year 1990-2016 and (Language English) and Humans]; 22 results. 28. CINAHL; 26 [Limit to: Publication Year 1990-2016 and (Language English)]; 4 results. 29. EMBASE; 25 [Limit to: Human and (Languages English) and (Year Published Last 26 Years)]; 77 results	1. Medline; (tumor OR tumour).ti,ab; 1038962 results. 2. Medline; (necrosis AND factor AND receptor AND associated AND periodic AND syndrome).ti,ab; 256 results. 3. Medline; (necrosis AND factor AND receptor-associated AND periodic AND syndrome).ti,ab; 229 results. 4. Medline; TRAPS.ti,ab; 12385 results. 5. Medline; 2 OR 3 OR 4; 12470 results. 6. Medline; 1 AND 5; 408 results. 7. Medline; (familial AND Hibernian AND fever).ti,ab; 18 results. 8. Medline; 6 OR 7; 421 results. 9. Medline; (canakinumab OR Ilaris).ti,ab; 238 results. 10. Medline; (Anakinra OR kineret).ti,ab; 1096 results. 11. Medline; (IL-1 AND block*).ti,ab; 3894 results. 12. Medline; 9 OR 10 OR 11; 4986 results. 13. Medline; 8 AND 12; 20 results. 14. Medline; 13 [Limit to: Publication Year 1990-2016 and (Language English) and Humans]; 16 results. 15. EMBASE; 13 [Limit to: Publication Year 1990-2016 and (Language English) and Humans]; 47 results. 16. EMBASE; Duplicate filtered: [13 [Limit to: Publication Year 1990-2016 and (Language English) and Humans]]; 47results.
4 HIDS	5 Schnitzler:
1. Medline; (Hyperimmunoglobulin AND D AND syndrome).ti,ab; 29 results. 2. Medline; HIDS.ti,ab; 180 results. 3. Medline; (hyper-immunoglobulin AND D AND syndrome).ti,ab; 10 results. 4. Medline; (hyper AND IgD AND syndrome).ti,ab; 132 results. 5. Medline; (hyper-IgD AND syndrome).ti,ab; 117 results. 6. Medline; (mevalonate AND kinase AND deficiency).ti,ab; 188 results. 7. Medline; MKD.ti,ab; 120 results. 8. Medline; 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7; 455 results. 9. Medline; (anakinra OR Kineret).ti,ab; 1096 results. 10. Medline; (canakinumab OR ilaris).ti,ab; 238 results. 11. Medline; (etanercept OR enbrel).ti,ab; 5177 results.	1. Medline; (schnitzler* AND syndrome).ti,ab; 206 results. 2. Medline; (Anakinra OR Kineret).ti,ab; 1096 results. 3. Medline; (Canakinumab OR Ilaris).ti,ab; 238 results. 4. Medline; 2 OR 3; 1248 results. 5. Medline; 1 AND 4; 61 results. 6. Medline; 5 [Limit to: Publication Year 1990-2016 and (Language English) and Humans]; 42 results.

12. Medline; 9 OR 10 OR 11; 6206 results. 13. Medline; 8 AND 12; 35 results. 14. Medline; 13 [Limit to: Publication Year 1990-2016 and (Language English) and Humans]; 26 results. 15. EMBASE; 13 [Limit to: Publication Year 1990-2016 and (Language English) and Humans]; 91 results. 16. CINAHL; 13 [Limit to: Publication Year 1990-2016 and (Language English) and Humans]; 0 results.	

11. Evidence selection

An initial review of abstracts was undertaken of each of the five searches, and papers excluded as follows:

Total results Excluded for*:	Search one – Anakinra (19 results)	Search Two – FMF (95 results)	Search Three – TRAPS (46 results)	Search four – HIDS (117 results)	Search five – Schnitzler's syndrome (42 results)
Size of study <4	4	24	7	30	20
Treatment relevance or duplicate	3	31	11	30	14
Conference abstract / not peer reviewed / letter / discussion piece	7	31	23	48	1
Total full papers requested for review	**5**	**9**	**5**	**9**	**7**
*NB exclusion on first filter: paper may also be eligible for exclusion for the other reasons, but was not counted twice in this filter.					

The second filter involved a quick review of the 35 remaining full papers and excluded for the following reasons:

- 4 more duplicates
- 5 papers whose results were already included in a systematic review below
- 8 Discussion papers or articles
- 3 not answering PICO
- 4 for retrospective case reviews which were poor quality as high potential for bias, and had <100 participants
- 2 not available

The total number of publications reviewed fully, considered relevant and included in this briefing:

- 1 RCT (double blinded)
- 2 prospective cohort study >4 participants
- 2 systematic reviews
- 3 retrospective case reviews of >100 cases (albeit high potential for bias)
- 1 retrospective case review <100 but specific for Schnitzler's syndrome

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