NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal consultation document

Anakinra for treating Still's disease

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using anakinra in the NHS in England. The appraisal committee has considered the evidence submitted by the company and the views of non-company consultees and commentators, clinical experts and patient experts.

This document has been prepared for consultation with the consultees. It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the consultees and commentators for this appraisal and the public. This document should be read along with the evidence (see the committee papers).

The appraisal committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

After consultation:

- The appraisal committee will meet again to consider the evidence, this appraisal consultation document and comments from the consultees.
- At that meeting, the committee will also consider comments made by people who are not consultees.
- After considering these comments, the committee will prepare the final appraisal document.
- Subject to any appeal by consultees, the final appraisal document may be used as the basis for NICE's guidance on using anakinra in the NHS in England.

For further details, see NICE's guide to the processes of technology appraisal.

The key dates for this appraisal are:

Closing date for comments: 27th January 2021

Second appraisal committee meeting: To be confirmed

Details of membership of the appraisal committee are given in section 6.

1 Recommendations

1.1 Anakinra is recommended as an option for treating Still's disease with moderate to high disease activity, or continued disease activity after non-steroidal anti-inflammatory drugs (NSAIDs) or glucocorticoids. It is only recommended for:

- adult-onset Still's disease that has responded inadequately to 2 or more conventional disease-modifying antirheumatic drugs (DMARDs)
- systemic juvenile idiopathic arthritis in people 8 months and older with a body weight of 10 kg or more that has not responded to at least 1 conventional DMARD.

1.2 This recommendation is not intended to affect treatment with anakinra that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop. In the case of children and young people, this decision should be made jointly by the clinician, the child or young person, and their parents or carers.

Why the committee made these recommendations

Still's disease is a rare systemic autoinflammatory condition. People who are 16 and under at diagnosis are considered to have systemic juvenile idiopathic arthritis, even in adulthood. People who are over 16 at diagnosis are considered to have adult-onset Still's disease. Treatment options for Still's disease include NSAIDs, corticosteroids, non-biological DMARDs and biological DMARDs such as tocilizumab and anakinra.

Clinical evidence about the efficacy of anakinra after treatment with NSAIDs and corticosteroids is highly uncertain. But it is reasonable to assume that it is as effective as tocilizumab. Cost-effectiveness estimates for anakinra are also uncertain because of issues with the company's economic model and the lack of robust clinical

evidence to support it. However, a comparison of the costs of anakinra and tocilizumab shows that they have similar weekly costs for:

- adult-onset Still's disease that has responded inadequately to 2 or more conventional DMARDs
- systemic juvenile idiopathic arthritis that has not responded to at least 1 conventional DMARDs.

Anakinra is therefore recommended for use in the NHS in these circumstances.

2 Information about anakinra

Marketing authorisation indication

2.1 Anakinra (Kineret, Sobi) is 'indicated in adults, adolescents, children and infants aged 8 months and older with a body weight of 10 kg or above for the treatment of Still's disease, including Systemic Juvenile Idiopathic Arthritis (sJIA) and Adult-Onset Still's Disease (AOSD), with active systemic features of moderate to high disease activity, or in patients with continued disease activity after treatment with non-steroidal anti-inflammatory drugs (NSAIDs) or glucocorticoids'. It can be given alone or with other anti-inflammatory drugs and disease-modifying antirheumatic drugs.

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics.

Price

2.3 The cost for 7 prefilled injections (each containing 100 mg anakinra per 0.67 ml) is £183.61, excluding VAT (BNF, accessed December 2020). The average cost of 1 year of treatment is £9,580.

3 Committee discussion

The appraisal committee considered evidence submitted by Sobi, a review of this submission by the evidence review group (ERG), NICE's technical report and responses from stakeholders. See the committee papers for full details of the evidence.

The appraisal committee was aware that 1 issue was resolved during the technical engagement stage. It agreed that canakinumab is not routinely used in the NHS for treating either systemic juvenile idiopathic arthritis (JIA) or adult-onset Still's disease (AOSD), so is not a relevant comparator for anakinra.

It recognised that there were remaining areas of uncertainty associated with the analyses presented (see technical report, table 2, page 25), and took these into account in its decision making. It discussed issues 1, 3, 4, 5, 6, and 7), which were outstanding after the technical engagement stage.

Clinical need

Still's disease substantially affects health-related quality of life

3.1 The patient and clinical experts explained that there is a considerable unmet need for people with systemic JIA and AOSD. The patient experts described that Still's disease is a highly debilitating condition affecting many aspects of life, including normal activities of everyday living, education and work opportunities, and personal relationships. A patient expert, who was diagnosed with Still's disease before biological disease-modifying antirheumatic drugs (DMARDs) were available, described their experience of having had multiple joint replacement surgeries from an early age. The committee heard that treatment with corticosteroids and conventional DMARDs such as methotrexate is associated with adverse reactions. These can affect quality of life, including important life decisions such as whether to have children (methotrexate is contraindicated in pregnancy). The committee concluded that Still's disease is a debilitating condition that substantially affects both physical and psychological aspects of health-related quality of life.

Clinical management

Clinicians and patients would prefer earlier access to biological DMARDs such as anakinra

3.2 The clinical experts explained that the NHS England clinical commissioning policy on anakinra and tocilizumab for ASOD and its policy statement on biologic therapies for the treatment of juvenile idiopathic arthritis do not reflect how clinicians would like to treat systemic JIA and AOSD. They provide funding for anakinra for people with:

- AOSD when the condition has not responded to 2 or more conventional DMARDs
- systemic JIA when the condition has not responded to tocilizumab, in line with NICE's technology appraisal guidance on tocilizumab.

This guidance recommends using tocilizumab to treat systemic JIA that has responded inadequately to non-steroidal anti-inflammatory drugs (NSAIDs), systemic corticosteroids and methotrexate. The clinical experts explained that greater flexibility to use biological DMARDs such as anakinra earlier in the treatment pathway would enable better outcomes for people with the condition. This is because it would result in quicker disease control that would better prevent progressive joint and systemic damage. One clinical expert suggested that the need to use conventional DMARDs before biological DMARDs can cause substantial delays in controlling Still's disease, and can lead to prolonged corticosteroid use. The company highlighted that the marketing authorisation allows anakinra to be used earlier in the pathway than the NHS England commissioning policies do. The committee heard that, by following the NHS England commissioning policies, people can wait up to 6 months before their condition is controlled because of the requirement to try multiple treatments before anakinra. The patient experts explained that using anakinra earlier in the pathway could dramatically improve quality of life through improved disease control and better long-term outcomes (such as

avoiding or delaying joint damage). The clinical experts further explained that there are different phenotypes in systemic JIA and AOSD. Some people present with mainly systemic disease, some with evidence of macrophage activation syndrome and some with a strong arthritic component. This complexity means that some symptoms might respond more to 1 specific biological DMARD than another. The committee concluded that clinicians would welcome the option to choose when and how to use biological DMARDs with NSAIDs, corticosteroids and conventional DMARDs according to disease phenotype. The aim would be to achieve more rapid disease control and improve outcomes.

Anakinra's use for macrophage activation syndrome is not within the remit of this appraisal

3.3 Using anakinra for macrophage activation syndrome falls outside of its marketing authorisation. The committee noted that the NHS England clinical commissioning policy for systemic JIA provides funding for anakinra for macrophage activation syndrome. The committee understood that the relevant part of the commissioning policy for macrophage activation syndrome in systemic JIA would continue to stand regardless of the outcome of this appraisal. NICE can only appraise a technology within its marketing authorisation, so the committee concluded that using anakinra in macrophage activation syndrome is not within the remit of this appraisal.

Clinical evidence

The clinical evidence for anakinra after conventional DMARDs is limited

3.4 The company's clinical-effectiveness evidence included:

- for systemic JIA: 2 randomised controlled trials comparing anakinra with placebo and 1 non-randomised registry study comparing it with tocilizumab
- for AOSD: 1 open-label randomised controlled trial comparing anakinra with conventional DMARDs.

The clinical trials were either open label or had a short, blinded phase followed by short open-label extensions. The placebo-controlled trials had very small patient numbers, which the committee heard was because of the rarity of Still's disease. The ERG noted that the results from these trials showed a good response in disease activity measures with anakinra. However, they were highly uncertain, mainly because of the small patient numbers. The trial limitations were acknowledged by the study authors and the company. The clinical experts explained that, because of the rarity of Still's disease, the low quantity and quality of the data are to be expected, and are unlikely to improve. The committee concluded that the evidence to support the clinical efficacy of anakinra after conventional DMARDs was limited because of the small patient numbers in the trials.

It is reasonable to assume that anakinra and tocilizumab have similar efficacy

3.5 The company submission stated that there was no direct trial evidence comparing anakinra with tocilizumab, but that a network meta-analysis (NMA) of clinical trials for systemic JIA included an indirect comparison between the 2 drugs. It explained that this suggested the treatments are similarly effective, and associated with the same adverse event profiles and stopping rates in the third-line setting (that is, after conventional DMARDs). The company did not include the results of the NMA in its economic model. This was because it considered that methodological differences between the included trials meant the results were not robust. The clinical experts explained that anakinra and tocilizumab are both biological DMARDs that target cytokines involved in the inflammation pathway. However, they noted that the drugs have slightly different mechanisms of action, and that anakinra targets interleukin-1 while tocilizumab targets interleukin-6. The clinical experts agreed that this difference does have implications for the way in which the drugs are used in clinical practice. This is because of the different phenotypes in systemic

JIA and AOSD (see section 3.2). Anakinra will often be preferred for presentations in which systemic features prevail, and tocilizumab will often be preferred when there are mainly arthritic joint features. The clinical experts added that, in many cases, it may be necessary to swap back and forth between these drugs to achieve disease control. The committee noted that the clinical experts considered anakinra and tocilizumab to be broadly equivalent in terms of efficacy and adverse reactions. The ERG also considered that it was reasonable to assume similar efficacy between the drugs based on the available evidence. The committee concluded that it was appropriate to consider that anakinra and tocilizumab are clinically equivalent.

There is no robust evidence to support using anakinra earlier in the treatment pathway

3.6 The clinical trials in the company submission (see section 3.4) only included people who had had treatment with NSAIDs, corticosteroids and conventional DMARDs. The trials were therefore aligned to current NHS practice (as set out in the NHS England commissioning policies). They were not aligned to the full breadth of the marketing authorisation, which was the company's preferred position for anakinra (that is, before conventional DMARDs). The company submitted supplementary evidence at technical engagement in support of using anakinra before conventional DMARDs. The anaSTILLs randomised placebo-controlled trial of anakinra met its primary endpoint but was stopped because of issues with recruitment. The company described how the results of this study showed the benefit of administering anakinra before conventional DMARDs. The committee noted the trial only included 6 people on anakinra and 5 people on placebo. It was aware that the other non-randomised studies submitted by the company support the emerging clinical view that interleukin-1 plays a particularly important role in early Still's disease. It was also aware that treatment with anakinra earlier in the pathway may lead to improved outcomes (see section 3.2). This is particularly so for systemic features of the condition, and is referred to as the 'window of opportunity' hypothesis.

The committee acknowledged the biological plausibility of the 'window of opportunity' hypothesis but concluded that there was no robust clinical evidence to support it.

Economic model

Treatment discontinuation rates in the company's model are not clinically plausible

3.7 In the company's model, changing from 1 treatment to another in the pathway was set at a fixed probability per weekly cycle for disease not in remission. The committee heard that the same probabilities were also used in NICE's technology appraisal of tocilizumab. The company presented several scenario analyses in which the rate was increased or decreased by 20% after 6 or 12 months, either for all treatments or just for biological DMARDs. The ERG explained that the fixed probability for changing from 1 treatment to another meant it was possible for a proportion of patients to remain on the same treatment for the whole time horizon of the model, without their disease going into remission. Based on its clinical expert advice, the ERG considered this to be clinically implausible. For example, it would mean that, of people having their first biological DMARD whose disease was not yet remission, over 55% would still be on this treatment after 1 year and about 33% would still on it after 2 years. The clinical experts explained that it is possible that someone might remain on a biological treatment for an extended period without their condition going into remission. This would be because of other treatment benefits, such as improved symptom control and quality of life. The company accepted that a limitation of its model was that it did not account for the full range of clinically plausible health states experienced by people with systemic JIA and AOSD. The ERG agreed that, other than remission, the benefits of remaining on a treatment were not captured in the model. The committee concluded that the way in which treatment discontinuation rates were modelled was not clinically plausible.

Disease remission rates in the company's model are not clinically plausible

3.8 The company model assumed that the probability of reaching disease remission with conventional DMARDs for people with chronic disease was 0%. It also presented a scenario analysis in which the probability was the same for people with chronic disease as monocyclic disease: a weekly remission probability of 12.56%. The ERG explained that, based on its own clinical expert advice, it is clinically implausible that nobody with chronic disease would reach remission with conventional DMARDs. The ERG explained that the remission rates for people with monocyclic disease had been taken from the Nordström et al. (2012) study. It highlighted that, in 20% of people in the conventional DMARDs arm of this study, their condition was in remission at 12 months. This suggests that conventional DMARDS are effective for some people. The clinical experts agreed that this was the case, and that there is good disease control with conventional DMARDs in some people, who then do not need biological DMARDs. However, they differed in their experience of the occurrence of remission in people with chronic disease having conventional DMARDs. One clinical expert estimated that remission would occur in less than 5% of people, assuming no prolonged corticosteroid use. Another considered that it would occur in 25% to 30% of people. The committee agreed that the second estimate seemed more plausible. It concluded that the remission rates for conventional DMARDs used in the company's model were unreliable.

The ERG's assumptions on the way tocilizumab is administered are appropriate

3.9 Tocilizumab can be administered intravenously or subcutaneously. The company model assumed that 50% of people would have it by intravenous injection, and 50% by subcutaneous injection. The ERG's clinical advisers considered this to be unlikely and that, for systemic JIA, about 20% of people would have it subcutaneously and about 80% intravenously. For AOSD, clinical advice to the ERG was that everyone

having tocilizumab would have it subcutaneously. The clinical experts explained that there are no available data on the proportions, but that the ERG's assumptions were broadly correct. The NHS England representative noted that subcutaneous injections can be administered either at home or in a community setting, rather than in hospital. This can be preferable in certain situations, and patient choice is important. People are increasingly choosing to have tocilizumab by subcutaneous rather than intravenous injection. The committee concluded that the ERG's assumptions on the way tocilizumab is administered were appropriate.

The company's economic model is unsuitable for decision making

3.10 The ERG explained that, as well as the issues about the highly uncertain evidence base that informed it, there were structural flaws in the model leading to implausible situations. These included:

- Treatment switching in the model was set at a fixed probability per weekly cycle for people whose disease was not in remission (see section 3.7). This made it possible for people to remain on a treatment that led to remission for the whole of the model time horizon.
- The model allowed people to start a treatment, for their condition to go into remission and relapse, and then for them return to the same treatment before their condition went into remission again. This was a perpetual loop for the whole model time horizon. In addition, the patient pathway loops in the model meant that, over time, people in specific health states became increasingly heterogeneous. The extent to which health state transition probabilities reflected the transition probabilities for the health state population decreased over time.
- It was assumed that 50% of people prescribed a biological DMARD would remain on that treatment during remission. However, when these people's condition relapsed, it was assumed that they would return to treatment with the same biological DMARD that they were taking before relapse. It was assumed that people would have the same probability of remission as they had before the relapse.

The ERG explained that, based on clinical advice, it considered these situations to be clinically implausible. The committee also questioned the validity of the model results. These showed a cost saving of about £25,000 over the model time horizon when anakinra was used about 6 months earlier in the treatment pathway compared with after conventional DMARDs. This cost saving could not be fully explained by the clinical experts. The committee acknowledged the structural flaws in the model and the lack of validity in the model results. It concluded that the company's economic model was not suitable for decision making.

Cost-minimisation analysis

A cost-minimisation analysis is sufficient for decision making

3.11 Because of its concerns over the lack of clinical evidence and structural flaws in the model, the ERG provided a cost-minimisation analysis. It based this analysis on the assumption of equal efficacy between anakinra and tocilizumab in treating AOSD and systemic JIA. The committee was considered that this was reasonable based on the clinical experts' opinions, and because there was no evidence of a difference in treatment effect (see section 3.5). The committee concluded that a cost-minimisation analysis was sufficient for decision making.

Cost-minimisation results

Anakinra has a similar weekly cost compared with tocilizumab

3.12 The ERG's cost-minimisation analysis considered the third-line treatment setting for anakinra (that is after conventional DMARDs) in both systemic JIA and AOSD. The analysis assumed that anakinra and tocilizumab had:

- equal efficacy
- the same side effect profiles
- the same treatment discontinuation rates.

The analysis included the costs of the different methods of

administration (see section 3.9) and monitoring costs. Tocilizumab has a confidential commercial arrangement, which was included in the analyses, but means that the exact results cannot be reported here. The committee concluded that the results suggest that anakinra has a similar weekly cost to tocilizumab for both systemic JIA and AOSD.

Other factors

There are no equality or social value judgement issues

3.13 The committee noted that no equality or social value judgement issues were identified.

Conclusion

Anakinra is recommended for routine commissioning

3.14 The committee acknowledged the need for biological treatment options for people with Still's disease. It concluded that the company's economic model was not suitable for decision making. However, it concluded that the cost-minimisation analysis suggested that anakinra has similar weekly costs compared with tocilizumab. Therefore, anakinra is recommended as an option for:

- systemic JIA when the disease has not responded to at least 1 conventional DMARD, and
- AOSD when the disease has responded inadequately to 2 or more conventional DMARDs.

4 Implementation

4.1 Section 7(6) of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.

4.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final appraisal document.

4.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has systemic juvenile idiopathic arthritis or adult-onset Still's disease and the doctor responsible for their care thinks that anakinra is the right treatment, it should be available for use, in line with NICE's recommendations.

5 Proposed date for review of guidance

5.1 NICE proposes that the guidance on this technology is considered for review by the guidance executive 3 years after publication of the guidance. NICE welcomes comment on this proposed date. The guidance executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Peter Selby
Chair, appraisal committee
December 2020

6 Appraisal committee members and NICE project team

Appraisal committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee C.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each appraisal committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Luke Cowie
Technical lead

Victoria Kelly
Technical adviser

Louise Jafferally
Project manager

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