# Clinical Commissioning Policy Statement
# Use of adalimumab for refractory chronic non-bacterial osteomyelitis / osteitis (CNO) (all ages) [201202P] (1926)

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## Commissioning position

### Summary

Adalimumab is not recommended to be available as a treatment option through routine commissioning for refractory chronic non-bacterial osteomyelitis/ osteitis (all ages).

## Information about adalimumab

### The intervention

Adalimumab (or best value biologic) is a biological medicine which falls under the class of drugs called tumour necrosis factor blockers. It targets immune cells to reduce inflammation in the body. It is commonly used to treat multiple inflammatory conditions such as rheumatoid arthritis and psoriasis. In most cases, the medication is administered at home by the patient/parent under the skin (subcutaneously). Biosimilars for adalimumab are now available, these are newer versions of the original drug which are just as effective and safe to use but are often cheaper.

## Committee discussion

Clinical Panel considered that the proposition reflected the evidence base presented, which was weak and supported the proposition progressing with a not for routine commissioning position.

See the committee papers (link) for full details of the evidence.

### The condition

Chronic non-bacterial osteomyelitis (CNO) is an auto-inflammatory condition that causes severe bone pain arising from inflammation of bone(s) without signs of an infection. CNO primarily affects children but can persist into adulthood. It covers a wide spectrum of disease ranging from time-limited mild inflammation affecting a single bone to severe chronically active or recurrent inflammation affecting multiple bones. Severe bone pain can result in functional impairment and CNO has a significant impact on quality of life, limiting the ability to take part in hobbies, activities of daily living and attending school (Zhao & Ferguson, 2018). In some cases, patients may continue to have impairment into adult life including bone deformity, disability and chronic pain resulting in significant morbidity (Roderick, Sen and Ramanan, 2018).

CNO is a rare disease, there are no current accurate data on incidence/prevalence in the UK. The incidence of CNO in Germany was reported to be 0.4 per 100,000 children (Jansson and Grote, 2011).

### Current treatments

There are no published standard treatment pathways in the UK. Generally non-steroidal anti-inflammatory (NSAIDs) are used first line. If patients fail to response, second line options include bisphosphonates, disease modified anti-rheumatic drugs (DMARDs) and tumour necrosis factor (TNF) blockers. The choice of second line depends on the availability of the drug, nature of the disease and physician/patient choice. Approximately 8-12% may be resistant

to first and second line treatment, requiring TNF blockers (Bhat et al, 2018, Kostik et al, 2019).

## Evidence summary

NHS England has concluded that there is not sufficient evidence to support the routine commissioning of this treatment for the indication.

### Clinical trial evidence

Three papers were presented for review. All three papers are cohort studies. Paper 1 is a retrospective analysis of an international web registry. Paper 2 is a retrospective analysis of three tertiary services in the UK. Paper 3 is a retrospective analysis of one tertiary referral centre in Germany.

### Paper 1: Girshick et al, 2018

### The multifaceted presentation of chronic recurrent multifocal osteomyelitis: a series of 486 cases from the Eurofever international registry

***Background:*** This paper reports a retrospective analysis of data collected from 486 patients (455 children and 31 adults) with chronic non-bacterial osteomyelitis from 19 countries held in an international web registry. The criteria for inclusion in the registry were mono-, oligo- or multifocal inflammatory bone lesion and duration of complaints for >6 weeks, exclusion criteria included infection and malignancy.

Treatment modality used and its response was recorded. Complete response was noted in patients with complete control of clinical manifestations and normalisation of laboratory parameters and imaging. Partial response was noted in patients with persistence of some clinical manifestations or perturbation of laboratory examinations and imaging. This was a physician dependent decision.

***Results:*** 74% (n=361/486) of patients received NSAIDs as first line treatment. 39% of these patients (n=141/361) displayed remission and 52% (n=188/361) had a partial response. 1.6% (n=8/486) of patients in the registry were treated with adalimumab as second line treatment. 4/8 patients who received adalimumab had a complete response. The other 4 patients had a partial response.

Other treatment options that were used as second line included glucocorticoids (n=112, 37% complete response, 54% partial response), sulfasalazine (n=47, 38% complete response, 49% partial response), methotrexate (n=58, 22% complete response, 50% partial response), etanercept (n=17, 41% complete response, 29% partial response), bisphosphonates (n=61, 51% complete response, 46% partial response), infliximab (n=9, 33% complete response, 44% partial response) and anakinra (n=4, 50% complete response, 25% partial response). Adverse events were not recorded.

It was not possible to define the particular effect of any one treatment with regards to concomitant or parallel medication, duration and intensity of medication from this study. None of the patients in the study were treated in centres in the UK.

### Paper 2: Bhat et al, 2018

### Chronic non bacterial osteitis- a multicentre study

***Background:*** This paper presents a retrospective analysis of data from 131 children with chronic non-bacterial osteomyelitis (Bristol diagnostic criteria applied retrospectively) who attended three tertiary services in the UK. Treatment modality used and its response was recorded. Remission was described as either clinical or radiological. Clinical remission meant subsidence of pain, swelling or constitutional symptoms. Radiological remission was defined as reduction of activity or reduction in number of radiological lesions.

***Results:*** NSAIDs were used first line (n=107/131) with a 58% observed response. TNF inhibitors were used if patients failed other agents. 11 patients in total received adalimumab as

second line treatment. Bhat et al, 2018 reported that 91% (n=10/11) of patients who received adalimumab as second line treatment showed signs of response. Response to treatment was based on the interpretation of the treating clinician.

Other treatment modalities included bisphosphonates (n=87, 69% observed response rate for clinical remission and 62% observed response rate for clinical and radiological remission), methotrexate (n=18, 44% observed response rate), corticosteroids (n=13, 80% observed response rate), infliximab (n=8, 88% observed response rate), sulfasalazine (n=3, 67% observed response rate), etanercept (n=1, 100% observed response rate) and mesalazine (n=1, 100% observed response rate). Adverse events were not recorded.

**Paper 3: Schnabel et al, 2017**
**Treatment Response and Long-term Outcomes in Children with Chronic Non-bacterial Osteomyelitis**

***Background:*** This paper is a retrospective analysis of data from 56 children with CNO attending one tertiary referral centre in Germany who were followed up over a 24-month period. Disease activity was recorded at 0, 3, 6, 12 and 24 months, which included clinical symptoms and objective measures such as inflammatory markers and lesions on imaging. Full clinical remission was defined by the absence of subjective and objective signs of inflammation. Partial clinical remission was defined as overall subjective improvement and reduction of inflammatory variables.

***Results:*** NSAIDs were exclusively used first line in the majority of patients (n=44/56). This was beneficial (complete or partial response) in all 44 patients at 3 months. At 2 years, 50% of these patients had relapsed. Treatment was escalated to corticosteroids, all patients (n=19) experienced clinical improvement after 2 weeks (complete or partial remission). 21% (n=4) relapsed or deteriorated by 3 months and 45% (n=4) after 1 year.

7 patients received TNF inhibitors as third line therapy if they had a poor response to NSAIDs and corticosteroids. All of these patients were diagnosed with chronically active disease (chronic recurrent multifocal osteomyelitis with vertebral involvement in 5 and associated arthritis in 4). Of these 7 patients, 6 patients received etanercept and 1 received adalimumab. Results are not presented separately for the patient who received adalimumab.

3/7 patients who received a TNF inhibitor following a poor response to NSAIDs and corticosteroids achieved complete remission at 3 months. 2/7 patients who received a TNF inhibitor achieved partial remission at 3 months. Remission remained stable at 12 months in these 5 patients. 2 patients developed side effects and discontinued treatment.

Other second line treatment options included bisphosphonates (n=8, 50% complete response and 50% partial response at 3 months). Data for 6 patients were available at 24 months, 5 had achieved completed remission and 1 partial.

**Adverse events**

Safety profile as per summary of product characteristics (SmPC, 2020).

**Conclusion**

The evidence reviewed consisted of retrospective studies with low patient numbers. There were no randomised controlled trials identified in this field and there is unlikely to be in the near future given the rarity of the disease. Although the study results were promising, they were not sufficient to support the routine commissioning of adalimumab for refractory CNO. Further research is recommended in this area with careful consideration for clear, robust outcome measures.

## Policy review date

This is a policy statement, which means that the full process of policy production has been abridged: a full independent evidence review has not been conducted; and public consultation has not been undertaken. If a review is needed due to a new evidence base then a new Preliminary Policy Proposal needs to be submitted by contacting england.CET@nhs.net.

## Equality Statement

Promoting equality and addressing health inequalities are at the heart of NHS England's values. Throughout the development of the policies and processes cited in this document, we have:

- Given due regard to the need to eliminate discrimination, harassment and victimisation, to advance equality of opportunity, and to foster good relations between people who share a relevant protected characteristic (as cited under the Equality Act 2010) and those who do not share it; and

- Given regard to the need to reduce inequalities between patients in access to and outcomes from healthcare services and to ensure services are provided in an integrated way where this might reduce health inequalities

## Definitions

| Term | Definition |
|---|---|
| Biosimilar | A biosimilar is a similar version of an original biological medicine. Adalimumab biosimilars are equally safe and effective in reducing inflammation as Humira (the original adalimumab medicine). |
| Bisphosphonate | A class of drugs used to prevent the loss of bone density, they are usually used in patients with osteoporosis. |
| Disease modifying anti-rheumatic drugs (DMARDs) | DMARDs are a group of medications commonly used in patients with rheumatoid conditions. They work to slow down disease progression and include azathioprine, ciclosporin, leflunomide, methotrexate and mycophenolate mofetil. These agents, also commonly referred to as immunosuppressive therapies are also widely used in a variety of other inflammatory conditions including vasculitis. |
| Incidence | Incidence is a measure of the probability of occurrence of a given medical condition in a population within a specified time period |
| Prevalence | Proportion of a population found to be affected by a medical condition. |
| Tumour necrosis factor | Cell signalling protein involved in systemic inflammation. Adalimumab targets this directly to reduce inflammation. |

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