MANAGEMENT IN CONFIDENCE

CLINICAL PRIORITIES ADVISORY GROUP
30 November 2020

Agenda Item No	2.2
National Programme	Internal Medicine
Clinical Reference Group	Specialised Rheumatology
URN	1926

Title
Use of Adalimumab for refractory chronic non-bacterial osteomyelitis / osteitis (CNO) (all ages)

Actions Requested	1. Support the adoption of the policy proposition
	2. Recommend its approval as an IYSD

Proposition
This policy statement proposition is recommended as not for routine commissioning. The proposition considered Adalimumab (a biological monoclonal antibody) to treat refractory chronic non-bacterial osteomyelitis (CNO) for all ages. CNO is a rare auto-inflammatory condition that causes severe bone pain. CNO primarily affects children but can persist into adulthood or present in adult life. It covers a wide spectrum of disease ranging from time-limited mild inflammation affecting a single bone to severe chronic or recurrent inflammation affecting multiple bones. A rapid three paper review of the evidence was conducted to inform the decision. Further research is recommended in this area to develop robust outcome measures.

Clinical Panel recommendation
The Clinical Panel recommended that the policy progress as a not for routine commissioning statement.

The committee is asked to receive the following assurance:	
1.	The Head of Clinical Effectiveness confirms the proposal has completed the appropriate sequence of governance steps and includes an: Evidence Review; Clinical Panel Report.
2.	The Head of Acute Programmes confirms the proposition is supported by an: Impact Assessment; Engagement Report; Equality and Health Inequalities Impact Assessment; Clinical Policy Proposition. The relevant National Programme of Care has approved these reports.

3.	The Director of Finance (Specialised Commissioning) confirms that the impact assessment has reasonably estimated a) the incremental cost and b) the budget impact of the proposal.
4.	The Clinical Programmes Director (Specialised Commissioning) confirms that the service and operational impacts have been completed.

The following documents are included (others available on request):	
1.	Clinical Policy Proposition
2.	Engagement Report
3.	Evidence Summary: 3 papers
4.	Clinical Panel Report
5.	Equality and Health Inequalities Impact Assessment

No	Metric	Summary from evidence review
1.	Survival	Not reported
2.	Progression free survival	Not reported
3.	Mobility	Not reported
4.	Self-care	Not reported
5.	Usual activities	Not reported
6.	Pain	Not reported
7.	Anxiety / Depression	Not reported
8.	Replacement of more toxic treatment	Not reported
9.	Dependency on care giver / supporting independence	Not reported
10.	Safety	Not reported
11.	Delivery of intervention	No evidence available

No	Metric	Summary from evidence review
1.	Complete response	Complete response is an outcome evaluating how well a patient has responded to the intervention of interest. A complete response is the desired effect of the drug, it denotes complete control of clinical manifestations and normalisation of laboratory parameters and imaging. Girschick et al, 2018 reported that 4/8 patients who received adalimumab as second line treatment had a complete response.

		There were several limitations with this study, it was a retrospective study with very low patient numbers. There was no comparative treatment and it is unclear whether patients were on concomitant medication whilst taking adalimumab. Weaknesses in the study's design and conduct mean it is subject to bias and confounding, is difficult to interpret and cannot support firm conclusions.
2	Partial response	Partial response is an outcome evaluating how well a patient has responded to the intervention of interest. Partial response was noted in patients with persistence of some clinical manifestations or perturbation of laboratory examinations and imaging. Girschick et al, 2018 reported that 4/8 patients who received adalimumab as second line treatment had a partial response. As above, see limitations for Girschick et al, 2018. The outcome of interest was a subjective physician dependent decision.
3.	No response	No response is an outcome evaluating how well a patient has responded to the intervention of interest. No response/failure denoted an absence of any substantial impact on disease activity. Girschick et al, 2018 reported that 0/8 patients who received adalimumab as second line treatment had no response. As above, see limitations for Girschick et al, 2018. The outcome of interest was a subjective physician dependent decision.
4	Complete remission	Complete remission is an outcome evaluating how well a patient has responded to the intervention of interest. Complete remission was defined by the absence of subjective and objective signs of inflammation. In Schnabel et al, 2017, 7 patients received TNF inhibitors (one received adalimumab in this group) as third line therapy if they had a poor response to NSAIDs and corticosteroids. Disease activity was recorded at 0, 3, 6, 12 and 24 months. 3/7 patients who received a TNF alpha inhibitor achieved complete remission. Remission remained stable at 12 months in these 3 patients. No separate analysis is presented for the patient who received adalimumab. This was a retrospective study with low patient numbers at one single centre in Germany. No direct comparator was included in the study design and the outcome measure was partly subjective. Weaknesses in the study's design and conduct mean it is subject to bias and confounding, is difficult to interpret and cannot support firm conclusions

5	Partial remission	Partial remission is an outcome evaluating how well a patient has responded to the intervention of interest. Partial clinical remission was defined as overall subjective improvement and reduction of inflammatory variables. In Schnabel et al, 2017, 7 patients received TNF inhibitors (one received adalimumab in this group) as third line therapy if they had a poor response to NSAIDs and corticosteroids. Disease activity was recorded at 0, 3, 6, 12 and 24 months. 2/7 patients who received a TNF inhibitor achieved partial remission at 3 months. Remission remained stable at 12 months in these 2 patients. No separate analysis is presented for the patient who received adalimumab. See above limitations for Schnabel et al, 2017.
6.	Inefficacy	Inefficacy is an outcome evaluating how well a patient has responded to the intervention of interest. Inefficacy was defined by the absence of improvement or disease progression resulting in treatment escalation. In Schnabel et al, 2017, 7 patients received TNF inhibitors (one received adalimumab in this group) as third line therapy if they had a poor response to NSAIDs and corticosteroids. Disease activity was recorded at 0, 3, 6, 12 and 24 months. TNF inhibitor therapy was ineffective in 2/7 patients. No separate analysis is presented for the patient who received adalimumab. See above limitations for Schnabel et al, 2017.
7.	Signs of response	Signs of response is an outcome evaluating how well a patient has responded to the intervention of interest. This outcome was not well defined in Bhat et al, 2018 and was based on the interpretation of the treating clinician. Bhat et al, 2018 reported that 91% (n=10/11) of patients who received adalimumab as second line treatment showed signs of response. This was a retrospective analysis with very low patient numbers at three UK services. There was no direct comparator. The outcomes of interests were not well defined and were dependent on the treating physician. Weaknesses in the study's design and conduct mean it is subject to bias and confounding, is difficult to interpret and cannot support firm conclusions.

Considerations from review by Rare Disease Advisory Group
Not applicable.

Pharmaceutical considerations
The clinical commissioning policy statement proposition does not recommend the use of Adalimumab for refractory chronic non-bacterial osteomyelitis / osteitis. This would have been an off-label use of adalimumab.

Considerations from review by National Programme of Care
1) The proposal was considered via virtual sign off and received the full support of the Internal Medicine NPoC Assurance Meeting in November 2020.