NHS ENGLAND SPECIALISED SERVICES

CLINICAL PANEL REPORT

Date: 19 July 2023

Intervention: Human normal immunoglobulin

Indication: scleromyxedema (adults and post-pubescent children)

URN: 2270

Gateway: 2, Round 1

Programme: Internal Medicine

CRG: Specialised Rheumatology

Information provided to the Panel

Policy Proposition

Evidence Review completed by NICE

Clinical Priorities Advisory Group (CPAG) Summary Report

Evidence to Decision Making (EtD) Report

Equalities and Health Inequalities (EHIA) Assessment

Patient Impact Assessment (PIA) Report

Policy Working Group (PWG) Appendix

This Policy Proposition recommends the use of normal human immunoglobulin (Ig) (intravenous or subcutaneous) for treatment of scleromyxedema (adults and post-pubescent children). This is considered to be a very rare progressive condition that is characterised by pathological deposits of mucin in the skin and connective tissue causing progressive severe skin thickening which restricts joint movement, restricts swallowing and causes nutritional difficulties. The condition often involves systemic involvement, particularly affecting cardiovascular and neurological function and can cause cardiac arrythmias, seizures and coma. No standard therapies or treatment algorithms currently exist in England. This proposition recommends the off-label use of Ig in this indication.

The proposition and the supporting evidence were presented to Panel members. The very rare nature of the condition was outlined, with seven patients known to be treated in the UK in the last 25 years.

The evidence review included four studies, all case series, which included a total of 86 individuals. None of the studies directly compared Ig to a control group (placebo or active comparator). Limitations of the studies were highlighted in the evidence review summary.

Critical outcomes were identified as disease activity, systemic involvement/extracutaneous manifestations, health related quality of life (HRQL). All studies provided very low certainty evidence against each outcome, according to GRADE. For disease activity, all studies suggested that activity scores and the number of people with complete or partial response improved compared with baseline, up to a mean follow up of 4.3 years. One case series

reported improvement in 6 out of 8 participants regarding systemic involvement/extracutaneous manifestations. One case series reported a reduction in the health assessment questionnaire disability index after 1-2 weeks of receiving Ig treatment. This was not statistically significant.

Very low certainty evidence of improvement was found in the reporting of important outcomes – duration of response, withdrawal/reduction of other immunosuppressants, and progression to dermatoneuro syndrome.

No cost effectiveness studies were identified.

The proposition and supporting documents were considered and some amendments requested. It was raised that there is no prior approval form required to support this proposition as there is a national database in place and each patient's details would be entered into this. The database would need to be updated if this proposition is approved to be commissioned.

Conditional circumstances of treatment use are stated in the EtD and this has informed the criteria in the proposition.

EHIA – no amendments requested.

PIA – no amendments requested.

Recommendation

Clinical Panel agreed with the proposition and recommended this proceeds as a routine commissioning proposition. It was agreed that the requested revisions to the proposition would be approved via Chair's action.

Why the panel made these recommendations

Clinical Panel members noted that the intended population was extremely small. They acknowledged the difficulty in conducting high quality studies due to the very rare nature of the condition so very few participants were involved, and therefore did not expect there to be any better available evidence. The evidence and reported outcomes were considered carefully and debated. Panel members agreed that, given the context of the condition, sufficient clinical benefits demonstrated enough to support the commissioning position.

Documentation amendments required

Policy Proposition:

- Inclusion criteria –
    - The wording in bullet point 3 section needs to be amended to provide clarity on what is meant. It could be read that the patient may not be symptomatic but could be eligible for treatment.
    - Referral to post pubescent child should be removed. The PWG should consider if children younger than those post pubescent would ever need access to the treatment and revise the wording accordingly.
- Starting criteria –
    - the reference to the Medicines for Children Policy should be removed from the main text and put as a footnote.

- Stopping criteria –
    - There is reference to appendix 1 ‘can be found in the policy proposition document’ – this is the policy proposition document, so the wording needs to be amended to reflect that. This is also stated in the monitoring section and needs amendment.
- Recommended dose –
    - A starting dose of 2g/kg is stated with a footnote referring to uncertainty. PWG to consider this as Panel members agreed there should be flexibility for the clinician to decide and suggest a range of 1g/kg – 2g/kg, depending on the severity of the condition. The footnote could then state that 2g/kg is the dose reported in the evidence base.
    - Dose adjustment – amend the first sentence to state that dose adjustment should be considered at 3 months and at 6 months after starting treatment. If not responding to Ig at this point, then the proposition needs to clearly state that this treatment will be stopped and other treatment options considered.
- Monitoring –
    - Treatment response – within the 8 parameters listed, photographic record is considered to be a way of measuring a parameter and not a parameter in itself. PWG to review and remove as appropriate.
- Patient Pathway Figure 1 –
    - This would benefit from adding another box at the end to include follow up regimen.

Declarations of Interest of Panel Members: None received.

Panel Chair: Anthony Kessel, Clinical Director, National Clinical Policy, Specialised Commissioning

PWG Post Panel Comments and document amendments

The clinical policy team/PWG made the following amendments to the policy proposition document following clinical panel:

- Inclusion criteria: clarification to reflect that patients should be diagnosed according to the internationally used Rongioletti and Rebora classification, with the caveat that according to clinical experience and more recent literature, it is accepted that not all patients will have a monoclonal gammopathy. However, requirement for biopsy-proven diagnosis remains.
- Introduction section and starting criteria: the Medicines for Children Policy has been removed from the main text and put as a footnote.
- Stopping criteria and monitoring section: references to appendix 1 now read “can be found in this document”
- Stopping criteria: additional criterion that treatment should be stopped at 6 months if no response to treatment, as patients usually respond within this time frame
- Recommended dose: starting dose has been amended to a range of 1g/kg – 2g/kg, with a footnote to reflect evidence base
- Dose adjustment: amended to state that dose adjustment should be considered at 6 months.
- Monitoring: photographic record has been amended to clarify that this is used to assess papular involvement rather than being a parameter in itself
- Patient Pathway Figure 1: follow up regimen now included

Post panel amendments signed off by: Anthony Kessel, Clinical Director, National Clinical Policy, Specialised Commissioning