CLINICAL PRIORITIES ADVISORY GROUP
3 July 2024

Agenda Item No	2.1
National Programme	Internal Medicine
Clinical Reference Group	Specialised Rheumatology
URN	2271

Title
Human normal immunoglobulin for scleromyxedema (adults)

Actions Requested	1. Support the adoption of the policy proposition 2. Recommend its approval as an in year service development

Proposition
Scleromyxedema is a rare, severe skin disorder, the signs and symptoms of which include abnormal accumulation of mucin (naturally occurring proteins) under the skin. Mucins are usually associated with fighting infection. This buildup of mucin (mucinosis) causes abnormal lumps within the skin. The condition is also associated with an increased production of connective tissue cells which, whilst vital for maintaining the form and function of the body and its organs, an overproduction can lead to problems with organ function. The causes of Scleromyxedema are not known. Owing to the extremely rare nature of the condition there is a limited evidence base, and no standard therapies or treatment algorithms exist in England. Treatment options include phototherapy, and systemic immunosuppression. The proposed intervention is to prescribe human normal immunoglobulin to be given either as an addition to current treatment, or as an alternative. The treatment is administered by infusion either intravenously or under the skin (subcutaneously) (IVIg/SCIg). This policy would bring NHS treatment in line with European-wide practice, which recommends human normal immunoglobulin as first line treatment. Service delegation status – retained.

Clinical Panel recommendation

The Clinical Panel recommended that this progresses as a routine commissioning policy proposition, and that this triggers an amendment to the published immunoglobulin policy.

The committee is asked to receive the following assurance:	
1.	The Deputy Director of Clinical Effectiveness confirms the proposition has completed the appropriate sequence of governance steps and includes a: evidence review; Clinical Panel Report.
2.	The Deputy Director of Acute Programmes confirms the proposition is supported by a: integrated 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 proposition.
4.	The Director of Clinical Commissioning (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
4.	Clinical Panel Report
5.	Equality and Health Inequalities Impact Assessment

In the Population what is the clinical effectiveness and safety of the Intervention compared with Comparator?

Outcome	**Evidence statement**
Clinical effectiveness	
Critical outcomes	
Disease Activity **Certainty of evidence:** Very Low	This outcome is important to patients as it reflects how effective the treatment is compared to current standard of care and is a surrogate for control of symptoms and quality of life. In total, 4 case series provided evidence relating to disease activity in adults with scleromyxedema. One was designed to assess the acute response to IV immunoglobulin after 1 to 2 weeks, one with a mean follow up of 34 months, one with a mean follow up of 44 months, and one with a mean follow up of 4.3 years. In the case series (Guarneri et al. 2017) there were 5 male and 3 female participants with a mean age of 59 years, all participants were Caucasian. The mean duration of

	scleromyxedema in this case series was 19 months. Six of the 8 participants had attempted other immunomodulatory therapies that were stopped for unsatisfactory results. In the cases series (Mahevas et al. 2020) there were 17 male and 16 female participants with a mean age of 55 years. The study included people on all interventions for scleromyxedema. Results are reported in this review for the 25 people had IV immunoglobulin treatment alone. Fifteen people had IV immunoglobulin first line, 6 people second line, and 4 people third line. In the case series (Mecoli et al. 2020) there were 12 female and 3 male participants with a mean age of 53 years. Fourteen of the participants were Caucasian, 12 were receiving maintenance IV immunoglobulin, and 3 were treatment naïve. In the case series (Rongioletti et al. 2013) there were 17 male and 13 female participants with a mean age of 59 years. The study included people on all interventions for scleromyxedema. Results are reported in this review for the 11 people who had IV immunoglobulin treatment alone within a treatment period. Six people had IV immunoglobulin first line, 2 people second line, 2 people third line, and one person fifth line. Follow up 1 to 2 weeks: In the case series (Mecoli et al 2020) the following outcomes were reported: • Mean (SD) MMRSS scores (0 to 60) post treatment reduced from 13.6(±2.6) to 10.3(±1.9) (p=0.003) **(VERY LOW)** • Mean (SD) PGA scores post treatment reduced from 1.4(±0.2) to 1.1(±0.2) (p=0.100) **(VERY LOW)** • Mean (SD) body surface area % affected post treatment reduced from 36(±38%) to 25(±29%) (p=0.099) **(VERY LOW)** • Mean (SD) skin scale pain scores post treatment reduced from 1.8(±2.4) to 1.4(±2.4) (p=0.252) **(VERY LOW)** • Mean (SD) skin scale flexibility scores post treatment reduced from 5.4(±3.5) to 3.3(±3.1) (p=0.013). **(VERY LOW)** • Mean (SD) skin scale softening scores post treatment reduced from 4.9(±3.4) to 2.7(±2.5) (P=0.022) **(VERY LOW)** • Mean skin scale global (0 to 10) post treatment reduced from 4.5(±3.3) to 2.7(±2.4) (p=0.029) **(VERY LOW)** Follow up at 2 months to 11 years (mean 33.5 months) In the case series (Rongioletti et al. 2013) the following outcomes were reported: • First line: 3/6 achieved complete response, 3/6 achieved partial response • Second line: 0/2 achieved complete response, 2/2 achieved partial response

	• Third line: 0/2 achieved complete response, 2/2 achieved partial response • Fifth line: 0/1 achieved complete response, 1/1 achieved partial response **(VERY LOW)** Follow up at 15 months to 87 months (mean 44 months) In the case series (Guarneri et al. 2017) the following outcomes were reported: • 2/8 (25%) participants achieved complete response and 6/8 (75%) achieved partial response. No statistical analysis reported. **(VERY LOW)** • mRSSS (0 to 182) reduced from 82.38 (37 to 145, SD 40.76) to 14.88 (0 to 37, SD 12.99) (p=0.012). **(VERY LOW)** • 5 participants had partial improvement (score 1) and 3 had full improvement (score 2) in their PGA scores. **(VERY LOW)** Follow up at 6 months to 13 years (mean 4.3 years) In the case series (Mahevas et al. 2020) the following outcomes were reported: • First line (mean follow up 21 months): 10/15 achieved complete response, 5/15 achieved partial response • Second line (mean follow up 24 months): 2/6 achieved complete response, 4/6 achieved partial response • Third line (mean follow up 28 months): 0/4 achieved complete response, 4/4 achieved partial response **(VERY LOW)** **Very low certainty evidence from 4 case series suggests disease activity scores and the number of people who had complete or partial response improved in people with scleromyxedema treated with IV immunoglobulin. However, some outcomes did not reach statistical significance and it is unknown if any results are clinically meaningful.**
Systemic involvement/ extracutaneous manifestations **Certainty of evidence:** Very Low	This outcome is important to patients because systemic involvement is linked to severe and/or untreated disease and has a large impact on quality of life and function. In total one case series (Guarneri et al. 2017) provided evidence relating to systemic involvement with a mean follow up of 44 months. All systemic symptoms (including neurologic, dysphagia, dyspnoea, arthralgias) improved in 6/8 participants and 2/8 participants continued to experience arthralgias. **(VERY LOW)** **Very low certainty evidence from one case series provided evidence that systemic involvement and extracutaneous manifestations improved after treatment with IV immunoglobulin in 6/8 participants.**
Health related quality of life (HRQL) **Certainty of evidence:**	This outcome is important to patients because it provides a holistic evaluation and indication of the patient's general health and their perceived well-being and their ability to participate in activities of daily living. This outcome is therefore a key indicator of the patient's perspective of effectiveness of treatment.

Insert range	One case series (Mecoli et al 2020) provided evidence relating HRQL with a follow up period of 1 to 2 weeks. Mean (SD) HAQ-DI scores reduced after treatment with IV immunoglobulin from 0.62(±0.7) to 0.54(±0.2) (p=0.403). **(VERY LOW)** **Very low certainty evidence from one case series provided evidence that the mean HAQ-DI score reduced 1 to 2 weeks after treatment with IV immunoglobulin, but this was not statistically significant.**
Important outcomes	
Duration of clinical improvement or response to treatment **Certainty of evidence:** Very low	This outcome is important to patients because it gives an indicator of how long the effect of this intervention may last, and how long they can expect to be treated for. One case series (Guarneri et al. 2017) provided evidence of the duration of clinical improvement or response to treatment. Maintenance infusions (every 4 to 6 weeks) were needed in 6/8 participants to maintain disease control. **(VERY LOW)** Two participants who reached complete response, stopped treatment after 7 and 11 months but relapses occurred after 6 and 25 months, respectively, and IV immunoglobulin was restarted. 1/8 participant developed dermatoneuro syndrome after stopping IV immunoglobulin voluntarily; complete recovery of the neurological symptoms was seen after the reintroduction of IV immunoglobulin after one cycle in 3 weeks. **(VERY LOW)** **Very low certainty evidence from one case series showed 6/8 participants needed maintenance infusions to maintain disease control. The 2 participants who reached complete response stopped treatment after 7 and 11 months but relapses occurred after 6 and 25 months, respectively. Reintroduction of IV immunoglobulin was successful in both cases.**
Withdrawal or reduction of other immunosuppressive treatments **Certainty of evidence:** Very low	This outcome is important to patients because it reduces the burden of treatment and reduces the side effect potential of immunosuppressive medication. No evidence was identified for this outcome.
Progression to dermatoneuro syndrome **Certainty of evidence:** Very Low	This outcome is important to patients because it is one of the most severe complications of untreated disease and often causes intensive care admission and long-term morbidity and mortality if untreated. Two case series (Guarneri et al. 2017 and Mahevas et al. 2020) provided evidence of the progression to dermatoneuro syndrome.

	Follow up at mean 21 months • 4/15 people who had first line IV immunoglobulin had progressed to dermatoneuro syndrome, cardiac injury, or death • 1/6 people who had second line IV immunoglobulin had progressed to dermatoneuro syndrome, cardiac injury, or death **(VERY LOW)** Follow up at 15 months to 87 months (mean 44 months) • Two of 8 (25%) participants progressed to dermatoneuro syndrome (one person before IV immunoglobulin [spontaneously recovered], and one person after stopping IV immunoglobulin voluntarily [restarting IV immunoglobulin led to a complete recovery of the neurological involvement]). No statistical analysis reported. **(VERY LOW)** **Very low certainty evidence from one case series showed that 2/8 participants progressed to dermatoneuro syndrome and, in another case series, 4/15 participants who had IV immunoglobulin first line and 1/6 second line progressed to dermatoneuro syndrome, cardiac injury, or death.**
Hospital admissions **Certainty of evidence:** Not applicable	This can provide objective evidence of treatment response and is relevant to patients because it has a significant impact on their life and is related to disease severity. No evidence was identified for this outcome.
Survival **Certainty of evidence:** Not applicable	This outcome is important to patients because it reflects how long people live after treatment, although it does not provide information about their health and wellbeing during that time. No evidence was identified for this outcome.
Safety	
Adverse drug reactions **Certainty of evidence:** Very low	Safety is important to patients as it reflects the risks involved in what is likely to be a long-term treatment. This allows a risk benefit assessment to be undertaken. One case series (Guarneri et al. 2017) provided evidence of adverse drug events (number of people) after a mean follow up of 44 months. The case series reports 13 adverse events in 5 people. Asthenia (4), headache (3), exfoliative keratolysis (2), acute hypertensive episodes (1), fever (1), dizziness (1), hypotension (1). **(VERY LOW)** One case series (Mahevas et al. 2020) provided evidence of serious side effects during a mean follow up of 21 months. 1/15 people who had IV immunoglobulin first line had thrombosis. **(VERY LOW)**

	Very low certainty evidence from one case series showed that 13 adverse events occurred in 5 of 8 participants. Very low certainty evidence from one case series showed that 1/15 people had a serious side effect.

Abbreviations

HAQ-DI, health assessment questionnaire disability index; IV, intravenous; MMRSS, modification of the modified Rodnan skin score; mRSSS, modified Rodnan skin score for scleromyxedema; PGA, physician global assessment; SD, standard deviation

In people with scleromyxedema what is the cost-effectiveness of human normal immunoglobulin as monotherapy or in addition to current standard care compared to standard care alone?

Outcome	Evidence statement
Cost-effectiveness	**No evidence was identified for this outcome.**

From the evidence selected, are there any subgroups of patients that may benefit from intravenous or subcutaneous Ig more than the wider population of interest?

Outcome	Evidence statement
Response to treatment in people who were treatment naïve and in people on maintenance IV immunoglobulin	One case series (Mecoli et al 2020) provided evidence relating to treatment response in people who were treatment naïve and people who were on maintenance IV immunoglobulin. MMRSS reduced from 20.6±5.1 at baseline to 13.3±4.7 after treatment (p=0.002) in the treatment naïve group (n=3) and reduced from 11.9±10.4 to 9.5±8.1 (p=0.034) in the people on maintenance IV immunoglobulin (n=12). No statistical analyses comparing the two subgroups were reported. Mean skin scale flexibility (0 to 10) reduced from 7.4±1.0 at baseline to 0.5±0.5 after treatment in the treatment naïve group and reduced from 4.9±3.6 to 3.9±3.0 in the people on maintenance IV immunoglobulin. No statistical analyses reported. **This study provides evidence response to treatment in people who were treatment naïve and in people on maintenance IV immunoglobulin. Response to treatment was greater in people who were treatment naïve compared with people who were on maintenance IV immunoglobulin. However, no conclusions can be drawn.**

Patient Impact Summary

The condition has the following impacts on the patient's everyday life:

- **mobility:** The disease course is progressive, resulting in severe limitation in movement due to severe skin thickening and tightening leading to loss of range of motion in joints. Recurrent admissions, for example for dermatoneuro syndrome, cause deconditioning and loss of mobility. Cardiac and respiratory involvement are likely to negatively impact mobility due to shortness of breath, reduced exercise tolerance and syncope.
- **ability to provide self-care:** In addition to joint involvement as detailed above, connective tissue involvement may restrict swallowing, leading to feeding and nutritional difficulties. Systemic involvement can also cause respiratory symptoms, arrhythmias, seizures and encephalopathy. These complications of the disease will impact ability to undertake all usual activities.
- **undertaking usual activities:** Restriction to movement, swallowing, and feeding will impact ability to undertake all usual activities. Neurological involvement is likely to particularly impact usual activities. If there is severe systemic involvement requiring admissions due to seizures or dermatoneuro seizure these admissions will also interfere with usual activities.
- **experience of pain/discomfort:** skin symptoms can cause pruritus which causes discomfort for patients. Joints can become painful and movement becomes progressively restricted. Discomfort and pain are associated with whichever organ system is involved. For example, oesophageal dysmotility is associated with the condition, and will cause dysphagia and nutritional difficulties. Cardiac and respiratory involvement are also associated with discomfort due to shortness of breath, syncope, and reduced exercise tolerance.
- **experience of anxiety/depression:** The fact that this disease can severely affect multiple organ systems, including joints, and causes associated difficulties with mobility, daily activities and self-care, is likely to negatively impact mental health and cause or contribute to anxiety and depression. Furthermore, awareness of the morbidity and mortality associated with the condition may cause anxiety and/or depression. Skin involvement may cause body image changes and this can also contribute to negative impacts on mental wellbeing. The extreme rarity of the condition impacts patients, causes isolation and may make support difficult to find.

Further details of impact upon patients:

As several organ systems are often involved, and can be seriously affected, the impact upon patients is considerable. Furthermore, many of the complications require admission for treatment, for example dermatoneuro syndrome, and this has a significant impact on patients and carers.

Further details of impact upon carers:

As the disease can affect adults of middle age, it affects the working age population which can lead to a loss of household income and increasing care burden on family members. Carers are also impacted by the loss of mobility, decreased ability to self-care and recurrent admissions which the patient experiences.

Considerations from review by Rare Disease Advisory Group
RDAG supported the policy proposition (October 2023).

Pharmaceutical considerations
This clinical commissioning policy proposition is for the use of human normal immunoglobulin as a treatment option for scleromyxedema in adults. Use in children is enabled through the NHS England Commissioning Medicines for Children policy. All use of human normal immunoglobulins must be recorded on the national Medical Data Solutions and Services (MDSAS) human normal immunoglobulin database. The recommendation is outside of the marketing authorisations for human normal immunoglobulin therapies so use is off-label and Trust policy regarding unlicensed medicines should apply. Human normal immunoglobulin therapies are on the NHS Payment Scheme Annex A, that is, they are excluded drugs.

Considerations from review by National Programme of Care
The proposal received the full support of the Internal Medicine PoC in November 2023 and in March 2024