Clinical Commissioning Policy:

Human normal immunoglobulin for treatment of scleromyxedema (adults) [2271]

Summary

Human normal immunoglobulin is recommended to be available as a routine commissioning treatment option for scleromyxedema within the criteria set out in this document.

The policy is for adults in line with the findings from the evidence review[1].

Committee discussion

Clinical Panel considered the evidence base and the recommendation was made to progress the policy as for routine commissioning. Please see the Clinical Panel report for full details of Clinical Panel's discussion. See the committee papers for full details of the evidence.

The Clinical Priorities Advisory Group committee papers can be accessed here: Clinical commissioning policy: human normal immunoglobulin for treatment of scleromyxedema (adults) – NHS England

What we have decided

NHS England has carefully reviewed the evidence to treat scleromyxedema with Human normal immunoglobulin. We have concluded that there is enough evidence to make the treatment available at this time.

The evidence review which informs this commissioning position can be accessed here: Clinical commissioning policy: human normal immunoglobulin for treatment of scleromyxedema (adults) – NHS England

[1] Access for use in children is available in line with the Commissioning Medicines for Children in Specialised Services policy 170001/P (commissioning medicines children).

Plain language summary

About scleromyxedema

Scleromyxedema (scleromyxoedema) is an extremely rare condition involving pathological deposits of mucin in the skin and connective tissue. Mucins are a family of protein structures with a dense sugar-coating which are produced by epithelial cells that line the internal and external surfaces of the body. Scleromyxedema involves excess mucin accumulation, causing severe skin thickening and tightening leading to loss of range of motion in joints. Solid raised areas called papules can appear on the skin. Skin biopsy, where a small amount of skin is taken and examined under a microscope, is often used to diagnose the condition.

The disease course is progressive, and as well as affecting mobility, connective tissue involvement may restrict swallowing, leading to feeding and nutritional difficulties. Systemic involvement, which is when internal organs other than skin and connective tissues are involved, is often present in scleromyxedema. This can particularly affect cardiovascular and neurological function, causing heart rhythm abnormalities, seizures and coma respectively. These symptoms affect psychological wellbeing of patients. Scleromyxedema is associated with monoclonal gammopathy, which is when abnormal proteins (antibodies) are found in the blood.

About current treatment

Due 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. Some historically used immunosuppressives carry a high risk of adverse effects. In a recent international systematic review, intravenous immunoglobulin monotherapy was the most commonly used first line treatment option (Haber et al., 2020).

About human normal immunoglobulin

Immunoglobulins are proteins found within plasma, which is the liquid component of blood. Human normal immunoglobulin (Ig) is a blood product prepared from donor plasma. It can be given to patients through an infusion into the veins or underneath the skin as treatment for certain conditions. In this policy, Ig is being proposed as first, second or any line of treatment, and can be combined with other treatments or used alone which is known as monotherapy.

Epidemiology and needs assessment

Scleromyxedema is an extremely rare condition. A recent systematic literature review identified 185 patients worldwide (97 studies) with a mean age of 52 years and a gender ratio M:F of 1.16:1 (Haber et al., 2020).

Careful literature analysis was unable to estimate the prevalence and incidence in the UK; however, 7 patients with scleromyxedema have been seen in the last 25 years by the major national centre for scleromyxedema.

Implementation

NHS England will routinely commission human normal immunoglobulin as monotherapy or in addition to current standard care at any point in the treatment pathway for patients meeting the criteria outlined below.

Inclusion criteria

Patients will be eligible for Ig treatment if they fulfil **ALL** of the following criteria:

- Diagnosed with scleromyxedema following a biopsy by a joint rheumatology and dermatology clinic within a rheumatology or dermatology specialised centre with expertise in autoimmune connective tissue disease.
    - The diagnosis was made in line with the widely acknowledged scleromyxedema diagnostic classification (Rongioletti and Rebora, 2001) where the patient should have **ANY** three[2] of the four following criteria:
        - Generalised, papular and sclerodermoid eruption
        - Presence of monoclonal gammopathy
        - Absence of thyroid disease
        - Histological triad of mucin deposition, fibroblast proliferation and fibrosis as confirmed by biopsy

Exclusion criteria

Patients with contraindications to therapy with human normal immunoglobulin are not eligible for treatment.

Starting criteria

Patients must be discussed at a joint rheumatology and dermatology clinic within a rheumatology or dermatology centre with expertise in autoimmune connective tissue disease. The decision made should be documented.

Human normal immunoglobulin can be prescribed and delivered locally once a documented decision has been made as above. It can be given as monotherapy or in addition to current standard care, and used at any point in the treatment pathway.

A completed referral form is still required for use of Ig in all indications. Provider organisations must register all patients using prior approval processes and ensure internal trust monitoring arrangements are in place to capture patient outcomes.

[2] Acknowledging that there is a proportion of patients with a diagnosis of scleromyxedema who do not have a monoclonal gammopathy.

Recommended dose

Starting dose is 1-2g/kg[3] by ideal body weight intravenously or equivalent subcutaneous dose[4]. Treatment should initially be delivered at a frequency of every 4 weeks. Initially treatment should be delivered over 2-5 days[5]. The dose can be modified according to treatment response (please see monitoring section below).

Total treatment dose per course should be calculated and then rounded down to the nearest 10g dose which can be administered using whole vials. Note in an adult patient part vials should never be used. Where the dose is split over multiple days, the daily dose may differ.

Dose adjustment:

Dose adjustment should be considered at 3, 6 and 12 months after starting treatment. Decisions around dose adjustment should be made by the joint rheumatology and dermatology clinic within a rheumatology/dermatology specialised centre multi-disciplinary team with expertise in autoimmune connective tissue disease and should involve assessment of treatment response as detailed in the monitoring criteria below.

The dose can be reduced by increasing the interval between treatments up to 6 weekly rather than 4 weekly. Alternatively, the dose given during each infusion can be reduced from 2g/kg. The minimum effective clinical dose to maintain remission should be established for each individual patient.

Monitoring

Local guidelines should be followed for monitoring during and immediately after infusions or treatments.

Clinical response:

Patients must be assessed for clinical response and safety 3 months after starting treatment at the local treating centre. The local centre should continue to monitor patients for safety throughout the duration of treatment.

Treatment response:

At 3 months after starting treatment, 6 months after starting treatment, then at 12 months after starting treatment, patients should be assessed virtually or in person by the joint rheumatology and dermatology clinic within rheumatology/dermatology specialised centre multi-disciplinary team with expertise in autoimmune connective tissue disease, who started the treatment. Thereafter frequency of specialist centre follow up should be a clinical/MDT decision, involving the patient in the decision-making process as appropriate.

[3] Noting that there is uncertainty regarding optimal start dose and that the majority of the papers included in the evidence review use a start dose of 2g/kg.
[4] Noting limited evidence for subcutaneous (Sc) Ig in this indication, this route of administration is still recommended to be available in line with the immunoglobulin Commissioning Criteria Policy (CCP) in which both routes of administration of Ig are available for all indications, despite limited evidence for Sc use in some. This is based on clinical experience and plausibility and additionally helps to manage administration and demand.
[5] It is anticipated that at the start of treatment the duration of delivery shall be closer to the upper limit.

Treatment response should include MDT assessment of some or all of the following parameters:

- Modified Rodnan skin score
- Disease severity, for example, progression to dermatoneuro syndrome
- Papular involvement (for example, as assessed by papular count over the same 2x2cm^2 area, using a photographic record with the same views taken at intervals)
- Itch visual analogue score (VAS)
- Patient Global Assessment (VAS)
- Physician Global Assessment (VAS)
- Nutritional status

Guidance for MDTs to assess the above parameters and use the listed scoring systems can be found in appendix 1 of this document.

Stopping criteria

Treatment should be stopped if patients are found to meet any of the criteria outlined below:

- Worsening of disease activity
- Worsening of extracutaneous manifestations
- Worsening health related quality of life
- No treatment response (assessed as above) after at least 6 months of therapy

Scoring systems to assess these criteria are detailed in the monitoring section above and further guidance can be found in Appendix 1 of this document.

Patient pathway

Treatment with human normal Ig should be considered in patients with scleromyxedema as described in the implementation criteria above..

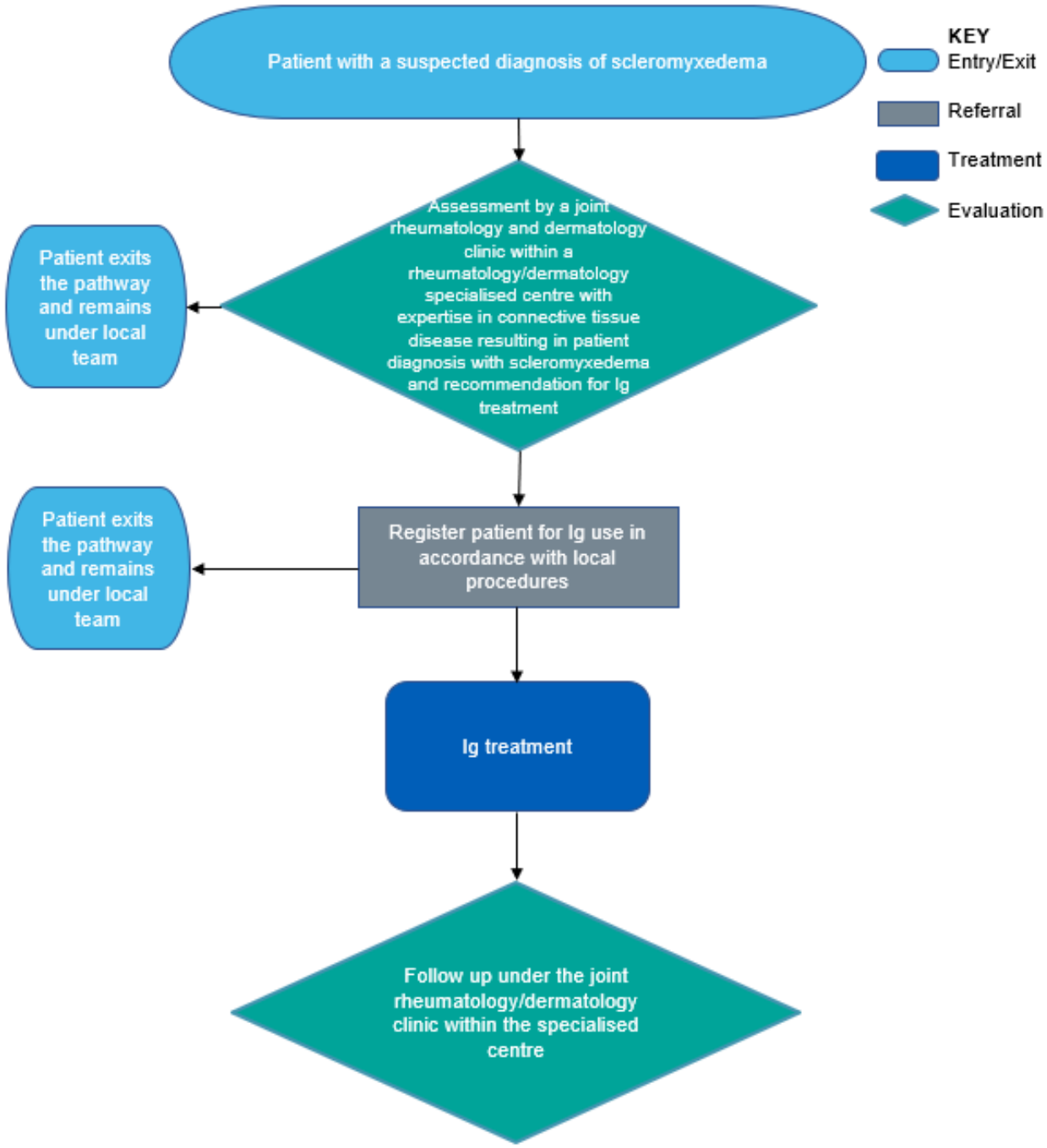


Figure 1: patient pathway

Governance arrangements

Provider organisations must register all patients using the MDSAS e-referral process. For urgent approvals in hours a process will need to be in place on the agreed pathway for approval. For those cases that require out of hours approval, trust Ig panels will have local processes in place, to ensure robust governance for retrospective panel approval. Panels will also be able to advise on dose optimisation and trials of treatment withdrawal.

Mechanism for funding

Reimbursement for the use of Ig for scleromyxedema meeting the criteria within this policy will be managed, through local contract agreements and terms, by the local NHS England Specialised Commissioning Teams.

Audit requirements

Patients should be registered and data on dose, route and frequency should be submitted to the MDSAS database annually. The following outcome measures should additionally be recorded:

- Absence or presence of systemic involvement, including progression to dermatoneuro syndrome as a marker of neurological involvement
- Hospital admissions per year relating to scleromyxedema

Policy review date

This document will be reviewed when information is received which indicates that the policy requires revision. 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.

Our policies provide access on the basis that the prices of therapies will be at or below the prices and commercial terms submitted for consideration at the time evaluated. NHS England reserves the right to review policies where the supplier of an intervention is no longer willing to supply the treatment to the NHS at or below this price and to review policies where the supplier is unable or unwilling to match price reductions in alternative therapies.

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

Dermatoneuro syndrome	A rare and potentially fatal complication of scleromyxedema associated with skin lesions, seizures, and coma and often requiring intensive care support.

Immunoglobulin	A protein that is made by B cells and plasma cells (a type of white blood cells) and helps the body fight infection
Mucin	A class of glycoproteins secreted by mucous membranes that are found within, for example, saliva and gastric juices
Monoclonal gammopathy	A condition in which an abnormal protein known as a monoclonal protein is found in the blood
Phototherapy	Phototherapy uses light waves to treat certain skin conditions

References

Haber R, Bachour J, El Gemayel M. Scleromyxedema treatment: a systematic review and update. Int J Dermatol. 2020 Oct;59(10):1191-1201. doi: 10.1111/ijd.14888. Epub 2020 May 2. PMID: 32358980.

Rongioletti F, Rebora A. Updated classification of papular mucinosis, lichen myxedematosus, and scleromyxedema. J Am Acad Dermatol. 2001 Feb;44(2):273-81. doi: 10.1067/mjd.2001.111630. PMID: 11174386.

Appendix 1

Monitoring for Scleromyxedema response to Human normal immunoglobulin:

The scoring systems and parameters outlined below are used to measure disease activity and severity and were used by studies included in the evidence review. MDTs assessing patient response to this treatment are encouraged to consider these systems to guide assessment.

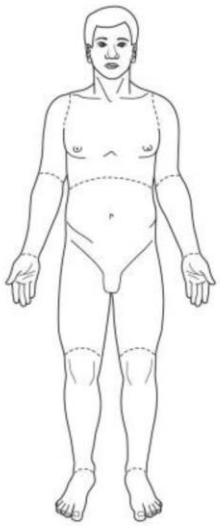
Modified Rodnan skin score:

The modified Rodnan Skin Score (MRSS) (Khanna et al, 2017) as seen in figure 1 involves assessment of skin thickness in 17 areas. A modified version for scleromyxedema was used by Mecoli (2020) and Guaneri (2017) to assess skin thickness and included the assessment of an additional three areas – the back, ears, and neck. Thus, a total of 20 areas are assessed, scored 0–3, for a total maximum score of 60.

Modified Rodnan Skin Score (MRSS) Document

Subject ID: _____

Date of Examination: _____



	Right				Left			
Fingers	0☐	1☐	2☐	3☐	0☐	1☐	2☐	3☐
Hands	0☐	1☐	2☐	3☐	0☐	1☐	2☐	3☐
Forearms	0☐	1☐	2☐	3☐	0☐	1☐	2☐	3☐
Upper Arms	0☐	1☐	2☐	3☐	0☐	1☐	2☐	3☐
Face			0☐	1☐	2☐	3☐		
Anterior Chest			0☐	1☐	2☐	3☐		
Abdomen			0☐	1☐	2☐	3☐		
Thighs	0☐	1☐	2☐	3☐	0☐	1☐	2☐	3☐
Legs	0☐	1☐	2☐	3☐	0☐	1☐	2☐	3☐
Feet	0☐	1☐	2☐	3☐	0☐	1☐	2☐	3☐
Column Totals								
Total:								
Key:	*0 – No Thickening*		*1 – Mild Thickening*		*2 – Moderate Thickening*		*3 – Severe Thickening*	
Notes:								

Examiner:

Printed Name: _____

Signature: _____ Date: _____

Figure 1: modified Rodnan skin score (Khanna et al, 2017)

Assessment of systemic involvement:

The following table can be used to aid assessment for systemic involvement as a marker of disease severity and activity. Neurological involvement includes dermatoneuro syndrome.

Organ system	Evidence of involvement (Y/N)	Evidence of progression (Y/N)
Neurological		
Cardiovascular		
Renal		
Gastrointestinal		

Papular involvement:

Papular involvement is a measure of disease activity and severity and should be assessed by papular count over the same 2x2cm^2 area.

Itch visual analogue scale:

Itch visual analogue scale (VAS), as demonstrated in figure 2, is a scale consisting of a 10cm long line and a single question. The score gives an indication of disease activity and severity.

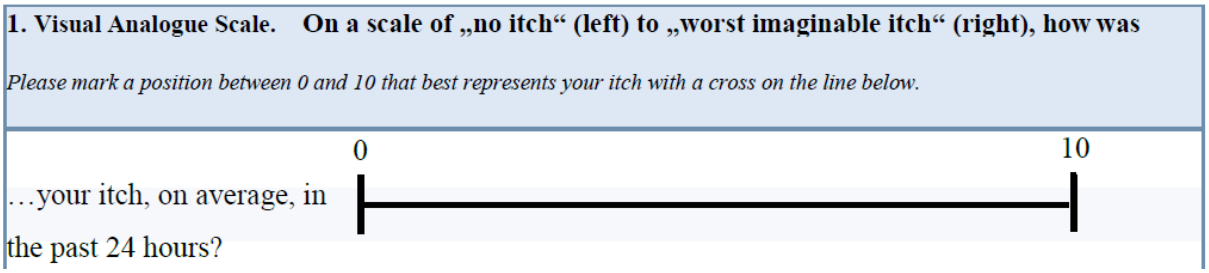


Figure 2: VAS for itch as adapted from Reich et al, 2016

Other measures of disease activity and severity include:

- Photographic record with the same views taken at intervals
- Patient Global Assessment (VAS) as assessed by the patient response to the following question: How do you assess your current disease severity”?
- Physician Global Assessment (VAS) as assessed by the treating clinician’s response to the following question: “How do you assess your patient’s current disease activity”?

References:

Khanna D, et al. Standardization of the modified Rodnan skin score for use in clinical trials of systemic sclerosis. J Scleroderma Relat Disord. 2017 Jan-Apr;2(1):11-18.

Reich A, Riepe C, Anastasiadou Z, Madrek K, Augustin M, Szepietowski JC, Ständer S. Itch assessment with visual analogue scale and numerical rating scale: determination of minimal clinically important difference in chronic itch. Acta Derm Venereol 2016; 96: 978–980.