NHS England Evidence Review:

Human normal immunoglobulin for scleromyxedema

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Contents

1. Introduction

This evidence review examines the clinical effectiveness, safety, and cost effectiveness of human normal immunoglobulin as monotherapy or in addition to current standard care for treating people with scleromyxedema compared with current standard care without immunoglobulin.

Immunoglobulin is licensed for use in primary and secondary immunodeficiencies and immunomodulation in several conditions. Its use in scleromyxedema is off label (Summary of product characteristics).

In addition, the review scope included the identification of possible subgroups of patients within the included studies who might benefit from treatment with immunoglobulin more than others, as well as the route of administration, dosage, frequency, and duration of treatment.

2. Executive summary of the review

This evidence review examines the clinical effectiveness, safety, and cost effectiveness of human normal immunoglobulin as monotherapy or in addition to current standard care for treating people with scleromyxedema compared with current standard care without immunoglobulin. The searches for evidence published since February 2013 were conducted on 14 February 2023 and identified 90 references. The titles and abstracts were screened and 5 full text papers were obtained and assessed for relevance.

Four case series were included in the evidence review (Guarneri et al. 2017, Mahevas et al. 2020, Mecoli et al. 2020, and Rongioletti et al. 2013). Guarneri et al. 2017 was based in Italy and included 8 participants who had completed at least 6 cycles of IV immunoglobulin infusions within the first 6 months of planned treatment. Mahevas et al. 2020 was based in France and included 33 people (25 received IV immunoglobulin). Mecoli et al. 2020 was based in the USA and included 15 participants (12 people on maintenance IV immunoglobulin, and 3 people who had not previously received IV immunoglobulin). Rongioletti et al. 2013 was a multi-centre study based in Europe and included 30 people (11 received IV immunoglobulin without concomitant interventions within a treatment period). Standard care in the studies was heterogenous. Other treatments included, but were not limited to, cyclosporine, azathioprine, cyclophosphamide, methotrexate, and steroids and IV immunoglobulin was used from first to fifth line. None of the studies directly compared immunoglobulin to a control group (either placebo or active comparator).

In terms of clinical effectiveness:

- **Disease activity.** Four case series provided very low certainty evidence for the critical outcome of disease activity, one was designed to assess the acute response to IV immunoglobulin after 1 to 2 weeks (12 people on maintenance therapy [mean 4.2 years], 3 people treatment naïve), 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. The studies suggest that disease activity scores and the number of people who had complete or partial response improved compared with baseline in people with scleromyxedema treated with IV immunoglobulin.
- **Systemic involvement/extracutaneous manifestations.** One case series provided very low certainty evidence for the critical outcome of systemic involvement/extracutaneous manifestations after treatment with IV immunoglobulin. Systemic involvement and extracutaneous manifestations improved in 6/8 participants (mean follow up of 44 months).
- **Health related quality of life.** One case series provided very low certainty evidence for the critical outcome of health related quality of life. The health assessment questionnaire disability index (HAQ-DI) score reduced 1 to 2 weeks after treatment with IV immunoglobulin, but this was not statistically significant.
- **Duration of clinical improvement or response to treatment.** One case series provided very low certainty evidence for the important outcome of duration of clinical improvement or response to treatment. It showed that 6/8 participants needed maintenance infusions to maintain disease control (mean follow up of 44 months). The 2 participants who obtained 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.** No evidence was identified for the important outcome of withdrawal or reduction of other immunosuppressive treatments.
- **Progression to dermatoneuro syndrome.** Two case series provided very low certainty evidence for the important outcome of progression to dermatoneuro syndrome. In one case series, 2/8 participants progressed to dermatoneuro syndrome (mean follow up of 44 months) and, in another case series, 4/15 participants who had IV immunoglobulin first line (mean follow up 21 months) and 1/6 who had IV immunoglobulin second line (mean follow up 24 months) progressed to dermatoneuro syndrome, cardiac injury, or death.
- **Hospital admissions.** No evidence was identified for the important outcome of hospital admission.
- **Survival.** No evidence was identified for the important outcome of survival.

In terms of safety:

- Two case series provided very low certainty evidence for safety. In one case series, there were 13 adverse events in 5 people after treatment with IV immunoglobulin during a mean follow up of 44 months. In one case series, 1/15 people who had IV immunoglobulin first line had a serious side effect (mean follow up 21 months).

In terms of cost effectiveness:

- No evidence was identified for cost effectiveness.

In terms of subgroups:

- One case series provided evidence for 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.

Limitations

The evidence review included 4 case series (Guarneri et al. 2017, Mahevas et al. 2020, Mecoli et al. 2020, and Rongioletti et al. 2013). It is difficult to conduct high quality studies in rare diseases such as scleromyxedema as there are few eligible participants and previous treatment regimens can differ substantially. All included studies have many limitations. For example, there were no comparators, Mahevas et al. 2020 and Rongioletti et al. 2013 were mainly retrospective, and the sample sizes were small (n=8, n=25, n=15, and n=11, respectively). All outcomes were considered to have very low certainty using modified GRADE.

No evidence was found comparing IV immunoglobulin with standard care. The studies were prospective and open label. Consequently, are subject to bias due to unblinding of participants and investigators, which can impact on patient reported outcomes or investigator assessed outcomes. Many of the reported outcomes could be considered subjective, including pain scores, Rodnan Skin Scores, and Physicians Global Assessment for disease severity (PGA), and are therefore subject to bias.

As with many small case series, the studies were not powered for statistical hypothesis testing and the data should be regarded as descriptive only. Case series are subject to bias, such as selection bias and observation bias, and confounding, and cannot prove that an intervention (such as IV immunoglobulin) caused a particular outcome, only that it is associated with that outcome.

In Mecoli et al. 2020, outcomes were reported 1 to 2 weeks after a single dose of IV immunoglobulin. Therefore, longer term outcomes, including complete or partial response, which are typically seen over several treatments, were not available for the 3 treatment naïve participants. Before treatment comparisons were also not available for the 12 participants on maintenance treatment. In Guarneri et al. 2017 (n=8), outcomes were reported at the last follow up assessment which ranged from 15 to 87 months. In this case series, 2/8 people achieved complete response and 6/8 people achieved partial response. In Mahevas et al. 2020, 10/15 people who had IV immunoglobulin first line achieved a complete response and 5/15 achieved a partial response. However, 2 of these people also experienced failure and 4 had dermatoneuro syndrome or died. Similarly for the people who had IV immunoglobulin second line 2/6 achieved complete response and 4/6 achieved partial response but one person experienced failure and one person had dermatoneuro syndrome or died. 'Failure' was not defined in the study and the definitions of response were subjective. In Rongioletti et al. 2013, 3/6 people who had IV immunoglobulin first line achieved complete response and 3/6 achieved partial response. The 5 people who had IV immunoglobulin second, third, or fifth line, all achieved partial response. Complete response was defined as disappearance of symptoms and no detectable findings on examination, however the outcome of partial response (decrease in skin changes and improvement in systemic symptoms) could be considered subjective.

The critical outcome of health related quality of life was only reported in the case series with a 1 to 2 week follow up (Mecoli et al. 2020). No significant difference was reported in the HAQ-DI. It is likely that a longer term follow up is needed to observe any differences.

Guarneri et al. 2017 reported adverse events over the mean 44 month follow up period. Five people experienced a total of 13 adverse events including asthenia, headache, exfoliative keratolysis, acute hypertensive episodes, fever, dizziness, and hypotension. These are consistent with the adverse events reported in the summary of product characteristics. Mahevas et al. 2020 reported a severe side effect of thrombosis during a mean 21 month follow up in 1/15 people who had IV immunoglobulin alone first line. Mecoli et al. 2020 had a shorter follow up period (1 to 2 weeks) and did not report any safety outcomes.

Mecoli et al. 2020 showed that people who were treatment naïve had a greater response to IV immunoglobulin, for the outcomes of MMRSS and skin flexibility, than people who were already on maintenance IV immunoglobulin. However, no statistical analyses were reported for between group differences, only 3 participants were treatment naïve, and outcomes were limited to a 1 to 2 week follow up.

No evidence was identified regarding cost effectiveness of immunoglobulin for people with scleromyxedema.

Conclusion

This evidence review found very low certainty evidence for the efficacy and safety of IV immunoglobulin for people with scleromyxedema.

Four prospective open label case series were included in the review Guarneri et al. 2017, Mahevas et al. 2020, Mecoli et al. 2020, and Rongioletti et al. 2013. The open label studies had no comparator and the sample sizes were small (n=8, n=25, n=15 and n=11). Mecoli et al. 2020

was designed to assess the acute response to IV immunoglobulin after 1 to 2 weeks (12 people on maintenance therapy [mean 4.2 years], 3 people treatment naïve), Rongioletti et al. 2013 had a mean follow up of 34 months, Guarneri et al. 2017 had a mean follow up of 44 months, and Mahevas et al. 2020 had a mean follow up of 4.3 years. As with all case series, unknown or unmeasured factors may have influenced the findings reported. Case series cannot prove cause and effect and should only be considered hypothesis generating.

The studies found very low certainty evidence that disease activity improved after IV immunoglobulin, although some outcomes were not statistically significant. Both Guarneri et al. 2017 (mean follow up 44 months) and Mecoli et al. 2020 (1 to 2 weeks after IV immunoglobulin) reported statistically significant improvements in mRSSS and MMRSS, respectively. Guarneri et al. 2017 found very low certainty evidence that 2/8 people achieved complete response and 6/8 people achieved partial response during a mean follow up of 44 months. In Mahevas et al. 2020, 10/15 people who had IV immunoglobulin first line achieved a complete response and 5/15 achieved a partial response during a mean follow up of 21 months. However, 2 of these people also experienced failure and 4 had dermatoneuro syndrome or died. Similarly for the people who had IV immunoglobulin second line 2/6 achieved complete response and 4/6 achieved partial response but one person experienced failure and one person had dermatoneuro syndrome or died. In Rongioletti et al. 2013, 3/6 people who had IV immunoglobulin first line achieved complete response and 3/6 achieved partial response. The 5 people who had IV immunoglobulin second, third, or fifth line, all achieved partial response.

Guarneri et al. 2017 provided very low certainty evidence that 5 people experienced a total of 13 adverse events during a mean follow of up 44 months. Mahevas et al. 2020 provided very low certainty evidence that one person who had IV immunoglobulin first line had the severe side effect of thrombosis during a mean 21 month follow up. None of the studies had a comparator group or were powered to detect differences in adverse events, therefore, larger studies with longer follow up durations are needed.

Regarding subgroups of patients who may benefit from treatment more than others, one case series (Mecoli et al 2020) provided evidence relating to treatment response in people who were treatment naïve and people who were already on maintenance IV immunoglobulin. Response to treatment (MMRSS and skin flexibility) was greater in people who were treatment naïve (n=3) compared with people who were on maintenance IV immunoglobulin (n=12). However, no statistical analyses comparing the two subgroups were reported.

No evidence was identified for the important outcomes of withdrawal or reduction of other immunosuppressive treatments, hospital admissions, or survival.

No evidence was identified regarding the cost effectiveness of IV immunoglobulin for people with scleromyxedema.

3. Methodology

Review questions

The review questions for this evidence review are:

1. In people with scleromyxedema what is the clinical effectiveness of human normal immunoglobulin as monotherapy or in addition to current standard care compared to standard care alone?
2. In people with scleromyxedema what is the safety of human normal immunoglobulin as monotherapy or in addition to current standard care compared to standard care alone?
3. 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?
4. 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?
5. From the evidence selected, what was the dose, frequency and route of administration of human normal immunoglobulin and duration of treatment?

See Appendix A for the full PICO document.

Review process

The methodology to undertake this review is specified by NHS England in its 'Guidance on conducting evidence reviews for Specialised Services Commissioning Products' (2020).

The searches for evidence were informed by the PICO document and were conducted on 14 February 2023.

See Appendix B for details of the search strategy.

Results from the literature searches were screened using their titles and abstracts for relevance against the criteria in the PICO document. Full text of potentially relevant studies were obtained and reviewed to determine whether they met the inclusion criteria for this evidence review.

See Appendix C for evidence selection details and Appendix D for the list of studies excluded from the review and the reasons for their exclusion.

Relevant details and outcomes were extracted from the included studies and were critically appraised using a checklist appropriate to the study design. See Appendices E and F for individual study and checklist details.

The available evidence was assessed by outcome for certainty using modified GRADE. See Appendix G for GRADE profiles.

4. Summary of included studies

Four papers were identified for inclusion (Guarneri et al. 2017, Mahevas et al. 2020, Mecoli et al. 2020 and Rongioletti et al. 2013). Table 1 provides a summary of these included studies and full details are given in Appendix E. The included studies were all case series Guarneri et al. 2017 included 8 people, Mahevas et al. 2020 included 33 people, Mecoli et al. 2020 included 15 people and Rongioletti et al. 2013 included 30 people.

Table 1: Summary of included studies

Study	Population	Intervention and comparison	Outcomes reported
Guarneri et al. 2017 Case series Italy	• Participants had characteristic skin findings of scleromyxedema confirmed by histopathology and the presence of monoclonal gammopathy • Participants must have completed at least six cycles of IV immunoglobulin within the first 6 months of planned treatment. • N=8 • No comparator group Baseline characteristics: • 5 males and 3 females • Mean age 59 years of age (range 35 to 70 years) • All participants were Caucasian • Mean duration of scleromyxedema was 19 months (range 6 to 37 months) • 6/8 participants had attempted other immunomodulatory therapies that were stopped for unsatisfactory results	**Intervention** IV immunoglobulin 2 g/kg per month, given over 4 or 5 days. IV immunoglobulin cycles were given every 4 to 6 weeks No concomitant treatments **Comparison** No comparator	**Critical outcome** • Disease activity • Systemic involvement/ extracutaneous manifestations **Important Outcomes** • Duration of clinical improvement or response to treatment • Progression to dermatoneuro syndrome • Adverse events
Mahevas et al. 2020 Case series France	• Participants had to have 3 or more of the 4 Rongioletti and Rebora criteria (1: papular eruption, 2: mucin deposition, fibroblast proliferation, fibrosis on skin histology, 3: monoclonal gammopathy, 4: the absence of thyroid disease) • N=25 (15 first line IV immunoglobulin, 6 second line, 4 third line) • No comparator group Baseline characteristics (reported for the entire cohort [n=33] and include people not on IV immunoglobulin alone, outcomes for these people are not reported in this review): • 17 males and 16 females • Mean (SD) age 55.4 years (±13.6) • Mean (SD) age at diagnosis 56.3 years (±13.6, range 28 to 78 years)	**Intervention** IV immunoglobulin 2 g/kg per month 15 people first line, 6 people second line, 4 people third line. **Comparison** No comparator	**Critical outcome** • Disease activity **Important Outcomes** • Progression to dermatoneuro syndrome • Adverse events
Mecoli et al. 2020 Case series USA	• People diagnosed with scleromyxedema with skin involvement. People were either newly diagnosed, treatment naive or undergoing IV immunoglobulin maintenance therapy • N=15 • No comparator group Baseline characteristics: • 3 males and 12 females	**Intervention** Single treatment of IV immunoglobulin 2 g/kg over a period ranging from 2 to 5 days All participants had IV immunoglobulin infusions every 4 weeks and then the interval increased to every 6 to 12 weeks once their improvement in skin involvement had plateaued	**Critical outcome** • Disease activity • Health related quality of life

	• Mean (SD) age 53 years of age (±11 years) • 14 participants were Caucasian • 12 participants were receiving maintenance IV immunoglobulin, and 3 participants were treatment naïve.	No concomitant treatments **Comparison** No comparator	
Rongioletti et al. 2012 Case series Europe, multi-centre	• People diagnosed with scleromyxedema with the following criteria (1: generalised papular and sclerodermoid eruption, 2: mucin deposition, fibroblast proliferation, and fibrosis, 3: monoclonal gammopathy, 4: the absence of thyroid disease) • N=11 (6 first line IV immunoglobulin,2 second line, 2 third line, one fifth line) • No comparator group Baseline characteristics (reported for the entire cohort [n=30] and include people not on IV immunoglobulin alone, outcomes for these people are not reported in this review): • 17 males and 13 females • Mean age 59 years (range 34 to 86) • Mean duration of scleromyxedema at diagnosis 9 months (range 1 to 60)	**Intervention** 'Usually' IV immunoglobulin 2 g/kg per month 6 people had IV immunoglobulin alone first line 2 people had IV immunoglobulin second line (after prednisone) 2 people had IV immunoglobulin third line (one person after prednisolone, followed by photopheresis; one person after methotrexate, followed by prednisone) One person had IV immunoglobulin fifth line (after cyclosporine, followed by azathioprine, followed by cyclophosphamide, followed by methotrexate and prednisone) **Comparison** No comparator	**Critical outcome** • Disease activity

Abbreviations

IV, intravenous

5. Results

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

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)	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.

Certainty of evidence: Very low	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 obtained 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 obtained 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:** Not applicable	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:** Not applicable	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.**

From the evidence selected, what was the dose, frequency, and route of administration of human normal immunoglobulin and duration of treatment?

Study	Dosage
Guarneri et al. 2017	IV immunoglobulin 2 g/kg per month, given over 4 or 5 days. IV immunoglobulin cycles were given every 4 to 6 weeks, depending on clinical response.
Mahevas et al. 2020	Mean dose of IV immunoglobulin 2 g/kg per month. No other information provided.
Mecoli et al. 2020	IV immunoglobulin 2 g/kg given over 2 to 5 days. After the first infusion (for which outcomes are reported after 1 to 2 weeks), all participants had IV immunoglobulin infusions every 4 weeks and then the interval increased to every 6 to 12 weeks once their improvement in skin involvement had plateaued.
Rongioletti et al. 2013	'Usually' 2 g/kg per month. No other information provided.

Abbreviations

IV, intravenous

6. Discussion

The evidence review included 4 case series (Guarneri et al. 2017, Mahevas et al. 2020, Mecoli et al. 2020, and Rongioletti et al. 2013). It is difficult to conduct high quality studies in rare diseases such as scleromyxedema as there are few eligible participants and previous treatment regimens can differ substantially. All included studies have many limitations. For example, there were no comparators, Mahevas et al. 2020 and Rongioletti et al. 2013 were mainly retrospective, and the sample sizes were small (n=8, n=25, n=15, and n=11, respectively). All outcomes were considered to have very low certainty using modified GRADE.

No evidence was found comparing IV immunoglobulin with standard care. The studies were prospective and open label. Consequently, are subject to bias due to unblinding of participants and investigators, which can impact on patient reported outcomes or investigator assessed outcomes. Many of the reported outcomes could be considered subjective, including pain scores, Rodnan Skin Scores, and PGA, and are therefore subject to bias.

As with many small case series, the studies were not powered for statistical hypothesis testing and the data should be regarded as descriptive only. Case series are subject to bias, such as selection bias and observation bias, and confounding, and cannot prove that an intervention (such as IV immunoglobulin) caused a particular outcome, only that it is associated with that outcome.

In Mecoli et al. 2020, outcomes were reported 1 to 2 weeks after a single dose of IV immunoglobulin. Therefore, longer term outcomes, including complete or partial response, which are typically seen over several treatments, were not available for the 3 treatment naïve participants. Before treatment comparisons were also not available for the 12 participants on maintenance treatment. In Guarneri et al. 2017 (n=8), outcomes were reported at the last follow up assessment which ranged from 15 to 87 months. In this case series, 2/8 people achieved complete response and 6/8 people achieved partial response. In Mahevas et al. 2020, 10/15 people who had IV immunoglobulin first line achieved a complete response and 5/15 achieved a partial response. However, 2 of these people also experienced failure and 4 had dermatoneuro syndrome or died. Similarly for the people who had IV immunoglobulin second line 2/6 achieved complete response and 4/6 achieved partial response but one person experienced failure and one person had dermatoneuro syndrome or died. ‘Failure’ was not defined in the study and the definitions of response were subjective. In Rongioletti et al. 2013, 3/6 people who had IV immunoglobulin first line achieved complete response and 3/6 achieved partial response. The 5 people who had IV immunoglobulin second, third, or fifth line, all achieved partial response. Complete response was defined as disappearance of symptoms and no detectable findings on examination, however the outcome of partial response (decrease in skin changes and improvement in systemic symptoms) could be considered subjective.

The critical outcome of health related quality of life was only reported in the case series with a 1 to 2 week follow up (Mecoli et al. 2020). No significant difference was reported in the HAQ-DI. It is likely that a longer term follow up is needed to observe any differences.

Guarneri et al. 2017 reported adverse events over the mean 44 month follow up period. Five people experienced a total of 13 adverse events including asthenia, headache, exfoliative keratolysis, acute hypertensive episodes, fever, dizziness, and hypotension. These are consistent with the adverse events reported in the summary of product characteristics. Mahevas et al. 2020 reported a severe side effect of thrombosis during a mean 21 month follow up in 1/15 people who had IV immunoglobulin alone first line. Mecoli et al. 2020 had a shorter follow up period (1 to 2 weeks) and did not report any safety outcomes.

Mecoli et al. 2020 showed that people who were treatment naïve had a greater response to IV immunoglobulin, for the outcomes of MMRSS and skin flexibility, than people who were already on maintenance IV immunoglobulin. However, no statistical analyses were reported for between group differences, only 3 participants were treatment naïve, and outcomes were limited to a 1 to 2 week follow up.

No evidence was identified regarding cost effectiveness of immunoglobulin for people with scleromyxedema.

7. Conclusion

This evidence review found very low certainty evidence for the efficacy and safety of IV immunoglobulin for people with scleromyxedema.

Four prospective open label case series were included in the review Guarneri et al. 2017, Mahevas et al. 2020, Mecoli et al. 2020, and Rongioletti et al. 2013. The open label studies had no comparator and the sample sizes were small (n=8, n=25, n=15 and n=11). Mecoli et al. 2020 was designed to assess the acute response to IV immunoglobulin after 1 to 2 weeks (12 people on maintenance therapy [mean 4.2 years], 3 people treatment naïve), Rongioletti et al. 2013 had a mean follow up of 34 months, Guarneri et al. 2017 had a mean follow up of 44 months, and Mahevas et al. 2020 had a mean follow up of 4.3 years. As with all case series, unknown or unmeasured factors may have influenced the findings reported. Case series cannot prove cause and effect and should only be considered hypothesis generating.

The studies found very low certainty evidence that disease activity improved after IV immunoglobulin, although some outcomes were not statistically significant. Both Guarneri et al. 2017 (mean follow up 44 months) and Mecoli et al. 2020 (1 to 2 weeks after IV immunoglobulin) reported statistically significant improvements in mRSSS and MMRSS, respectively. Guarneri et al. 2017 found very low certainty evidence that 2/8 people achieved complete response and 6/8 people achieved partial response during a mean follow up of 44 months. In Mahevas et al. 2020, 10/15 people who had IV immunoglobulin first line achieved a complete response and 5/15 achieved a partial response during a mean follow up of 21 months. However, 2 of these people also experienced failure and 4 had dermatoneuro syndrome or died. Similarly for the people who had IV immunoglobulin second line 2/6 achieved complete response and 4/6 achieved partial response but one person experienced failure and one person had dermatoneuro syndrome or died. In Rongioletti et al. 2013, 3/6 people who had IV immunoglobulin first line achieved complete response and 3/6 achieved partial response. The 5 people who had IV immunoglobulin second, third, or fifth line, all achieved partial response.

Guarneri et al. 2017 provided very low certainty evidence that 5 people experienced a total of 13 adverse events during a mean follow of up 44 months. Mahevas et al. 2020 provided very low certainty evidence that one person who had IV immunoglobulin first line had the severe side effect of thrombosis during a mean 21 month follow up. None of the studies had a comparator group or were powered to detect differences in adverse events, therefore, larger studies with longer follow up durations are needed.

Regarding subgroups of patients who may benefit from treatment more than others, one case series (Mecoli et al 2020) provided evidence relating to treatment response in people who were treatment naïve and people who were already on maintenance IV immunoglobulin. Response to treatment (MMRSS and skin flexibility) was greater in people who were treatment naïve (n=3) compared with people who were on maintenance IV immunoglobulin (n=12). However, no statistical analyses comparing the two subgroups were reported.

No evidence was identified for the important outcomes of withdrawal or reduction of other immunosuppressive treatments, hospital admissions, or survival.

No evidence was identified regarding the cost effectiveness of IV immunoglobulin for people with scleromyxedema.

Appendix A PICO document

The review questions for this evidence review are:

1. In people with scleromyxedema what is the clinical effectiveness of human normal immunoglobulin as monotherapy or in addition to current standard care compared to standard care alone?
2. In people with scleromyxedema what is the safety of human normal immunoglobulin as monotherapy or in addition to current standard care compared to standard care alone?
3. 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?
4. 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?
5. From the evidence selected, what was the dose, frequency, and route of administration of human normal immunoglobulin and duration of treatment?

P –Population and Indication	People with scleromyxedema [may be known as scleromyxoedema, generalised and sclero-dermoid lichen myxedematosus or Arndt–Gottron disease. The condition can be abbreviated to SMX]
I – Intervention	Human normal immunoglobulin (IVIg/SCIg) as monotherapy or in addition to current standard care Current standard care includes but is not limited to the following immunosuppressant options: cyclophosphamide, mycophenolate mofetil, methotrexate, hydroxychloroquine, melphalan, ciclosporin, thalidomide, lenalidomide, bortezomib, stem cell transplant, plasmapheresis, systemic corticosteroids. Phototherapy and other similar treatments may also be used. [Human normal immunoglobulin administered at any point in the treatment pathway] [Dose varies according to clinician choice and patient factors so all doses should be included. For information, the most frequently used starting dose is 2g/kg]
C – Comparator(s)	Current standard care [No defined standard of care exists in the UK in this patient group, however terms such as standard of care, optimised medical management may be used in the international literature]
O – Outcomes	**Clinical Effectiveness**

	Unless stated for the outcome, minimum clinically important differences (MCIDs) are unknown. Outcomes ideally measured at 6, 12, 24 months as well as long-term outcomes. *<u>Critical to decision making</u>* • **Disease activity** *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.* [Rodnan score/modified Rodnan score/modified Rodnan skin score/ modification of the modified Rodnan skin score/ modified Rodnan score system for scleromyxedema is often used to quantify disease activity in this condition. Disease activity may also be measured by body surface area involvement, skin thickening, skin flexibility, skin softening, pruritis, papular involvement, photographic assessment of disease activity, skin pain scale, skin scale global, visual analogue scale. Disease activity can be linked to presence and severity of skin symptoms. Patient reported measures as well as physician rated measures are both relevant. Physician global assessment (PGA) can be used as a generalised score of disease severity. Reduction in disease activity may also be termed as complete or partial clinical response/remission] • **Systemic involvement/extracutaneous manifestations** *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.* [Systemic involvement includes, but is not limited to; paraesthesia, neuropathy, carpal tunnel syndrome, cardiomyopathy, myocardial ischaemia, arthralgia, myositis, haematological malignancy, pulmonary fibrosis, dysphagia, central nervous system involvement (e.g coma, encephalopathy, seizures). Systemic involvement is also indicated by the presence of absence of symptoms such as difficulty swallowing, difficulty opening mouth, feeding or nutrition difficulties, shortness of breath and reduced mobility. Patient reported measures as well as physician rated measures are both relevant.] • **Health related quality of life (HRQL)**

	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 [Other terms used to describe or indicate quality of life include but are not limited to; patient-reported quality of life outcomes, health related quality of life. Examples of metrics to assess quality of life include but are not limited to: Short Form (SF-36), EuroQuality of Life Five Dimensions (EQ-5D), Dermatological life quality index (DLQI), Health assessment questionnaire-disability index (HAQ-DI). Other methods of assessing quality of life include but are not limited to subjective/self-reported/carer reported quality of life experiences.] *<u>Important to decision-making:</u>* • **Duration of clinical improvement or response to treatment** *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.* [Terms used to describe this may include, but are not limited to; time to recurrence, remission duration, time to relapse, time to flare.] • **Withdrawal or reduction of other immunosuppressive treatments** *This outcome is important to patients because it reduces the burden of treatment, and reduces the side effect potential of immunosuppressive medication* [Treatments include but are not limited to cyclophosphamide, mycophenolate mofetil, melphalan, ciclosporin, steroids.] • **Progression to dermatoneuro syndrome** *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.* [Dermatoneuro syndrome is defined as coma, encephalopathy and/or seizure (Mecoli et al., 2020)]

	• **Hospital admissions** *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.* [Admissions may be secondary to feeding and nutritional difficulties requiring, for example, PEG insertion. Dermatoneuro syndrome or other neurological involvement such as seizures can also lead to admission] • **Survival** *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.* [Other terms used to describe or indicate survival include, but are not limited to, overall survival, survival rate, freedom from death, death] **<u>Safety</u>** • **Complications of human normal immunoglobulin (IVIg/SCIg) therapy** *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* [Other terms used to describe or indicate safety include, but are not limited to; adverse events, serious/ major adverse events. This may include but is not limited to; death, aseptic meningitis, myocardial infarction, need for intensive care admission, haemolysis, fever, chills, rash, headache] **<u>Cost effectiveness</u>**
Inclusion criteria	
Study design	Systematic reviews, randomised controlled trials, controlled clinical trials, cohort studies. If no higher-level quality evidence is found, case series can be considered.
Language	English only
Patients	Human studies only

Age	All ages
Date limits	2013 – 2023
Exclusion criteria	
Publication type	Conference abstracts, non-systematic reviews, narrative reviews, commentaries, letters, editorials, pre prints and guidelines
Study design	Case reports, resource utilisation studies

Appendix B Search strategy

Medline, Embase and the Cochrane Library were searched limiting the search to papers published in English language in the last 10 years. Conference abstracts, commentaries, letters, editorials and case reports were excluded.

Search dates: 14 February 2023

Medline

1 Scleromyxedema/ 292
2 (Scleromyxedema* or scleromyxoedema* or scleromyxooedema* or arndt-gottron or (lichen adj (fibromucinoidosus or myxedematosus or myxoedematosus or myxooedematosus)) or ((mucinosis or myxedema or myxoedema or myxooedema) adj2 (papulosa or papulosum or popular))).tw. 589
3 or/1-2 654
4 Immunoglobulins, Intravenous/ or Immunoglobulins/ 59623
5 ((intravenous* or subcutanceous*) and immunoglobulin).tw. 14376
6 ("IVIg/SCIg" or (IVIg adj SCIg)).tw. 20
7 or/4-6 65696
8 3 and 7 82
9 limit 8 to english language 72
10 limit 9 to (letter or historical article or comment or editorial or news) 9
11 9 not 10 63
12 limit 11 to yr="2013 -Current" 37

Embase

1 scleromyxedema/ 841
2 (Scleromyxedema* or scleromyxoedema* or scleromyxooedema* or arndt-gottron or (lichen adj (fibromucinoidosus or myxedematosus or myxoedematosus or myxooedematosus)) or ((mucinosis or myxedema or myxoedema or myxooedema) adj2 (papulosa or papulosum or popular))).tw. 726
3 or/1-2 1018
4 immunoglobulin/ or human immunoglobulin/ 143312
5 ((intravenous* or subcutanceous*) and immunoglobulin).tw. 26426
6 ("IVIg/SCIg" or (IVIg adj SCIg)).tw. 49
7 or/4-6 148604
8 3 and 7 244
9 limit 8 to english language 218
10 9 not (letter or editorial).pt. 197
11 limit 10 to yr="2013 -Current" 116
12 (conference abstract* or conference review or conference paper or conference proceeding).db,pt,su. 5454108
13 11 not 12 92

Cochrane Library

#1 [mh ^Scleromyxedema] 0
#2 (Scleromyxedema* or scleromyxoedema* or scleromyxooedema* or arndt-gottron or (lichen NEAR (fibromucinoidosus or myxedematosus or myxoedematosus or

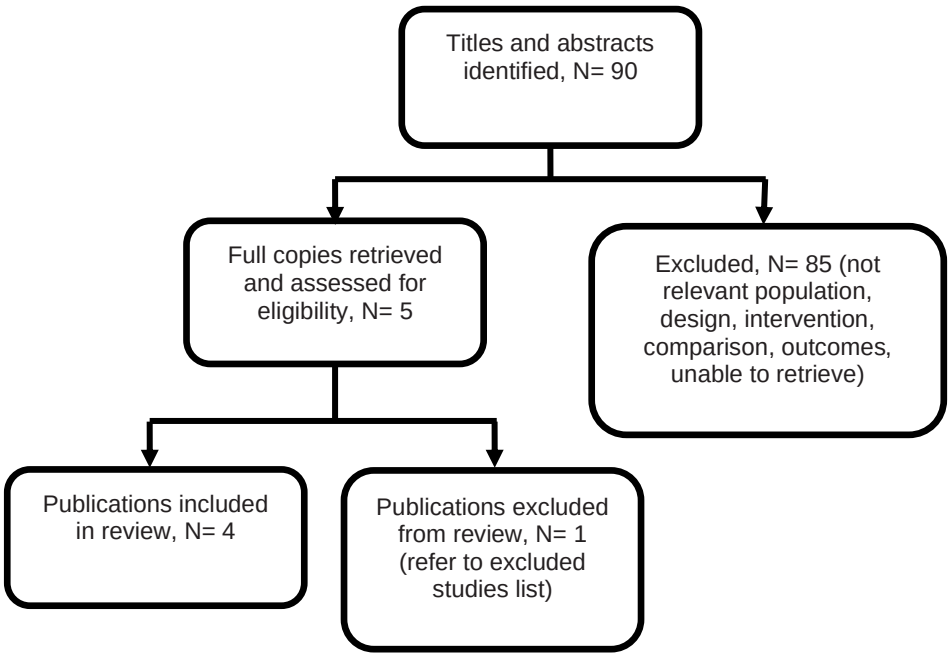
myxooedematosus)) or ((mucinosis or myxedema or myxoedema or myxooedema) NEAR/2 (papulosa or papulosum or popular))):ti,ab 0
#3 {or #1-#2} 0

- (did not continue with strategy as there were 0 results for condition)

Appendix C Evidence selection

The literature searches identified 90 references. These were screened using their titles and abstracts and 5 references were obtained in full text and assessed for relevance. Of these, 4 references are included in the evidence summary. The remaining reference was excluded and is listed in Appendix D.

Figure 1- Study selection flow diagram



References submitted with Preliminary Policy Proposal

Reference	Paper selection - decision and rationale if excluded
Mecoli, C. A., Talbot, C. C., Fava, A., Cheadle, C., Boin, F., Wigley, F. M., & Hummers, L. K. (2020). Clinical and Molecular Phenotyping in Scleromyxedema Pretreatment and Posttreatment With Intravenous Immunoglobulin. *Arthritis Care and Research*, *72*(6).	Included
Guarneri, A., Cioni, M., & Rongioletti, F. (2017). High-dose intravenous immunoglobulin therapy for scleromyxoedema: a prospective open-label clinical trial using an objective score of clinical evaluation system. *Journal of the European Academy of Dermatology and Venereology*, *31*(7).	Included
Rongioletti, F., Merlo, G., Cinotti, E., Fausti, V., Cozzani, E., Cribier, B., Metze, D., Calonje, E., Kanitakis, J., Kempf, W., Stefanato, C. M., Marinho, E., & Parodi, A. (2013). Scleromyxedema: A multicenter study of characteristics, comorbidities, course, and therapy in 30 patients. *Journal of the American Academy of Dermatology*, *69*(1).	Included

Appendix D Excluded studies table

Study reference	Reason for exclusion
Haber R, Bachour J, Gemayel M. (2020) Scleromyxedema treatment: a systematic review and update. International Journal of Dermatology, 59, 1191-1201.	Excluded – more complete evidence available from primary studies

Appendix E Evidence table

Study details	Population	Interventions	Study outcomes	Appraisal and funding
Full citation Guarneri A, Cioni M, Rongioletti F (2017) High-dose intravenous immunoglobulin therapy for scleromyxedema: a prospective open-label clinical trial using an objective score for clinical evaluation system. JEADV 32, 1157-1160 **Study location** Genoa, Italy **Study type** Prospective case series **Study aim** The aim of the study was 'to evaluate the safety and efficacy of high-dose intravenous immunoglobulin for the management of scleromyxedema prospectively using an objective score' **Study dates** Between January 2012 and March 2015	**Inclusion criteria** Participants had characteristic skin findings of scleromyxedema confirmed by histopathology and the presence of monoclonal gammopathy Participants needed to have completed at least 6 cycles of IV immunoglobulin infusion within the first 6 months of planned treatment **Exclusion Criteria** None reported **Total sample size** 8 people **No. of participants in each treatment group** All 8 participants received IV immunoglobulin **Baseline characteristics** 5 males and 3 females All 8 participant were Caucasian Mean age of 59 years of age (35 to 70 years) The mean duration of scleromyxedema was 19 months (6 to 37 months) 6/8 participants had attempted other immunomodulatory therapies that were stopped for unsatisfactory results.	**Interventions** 2 g/kg per month, given over 4 or 5 days. Depending on clinical response, IV immunoglobulin cycles were given every 4 to 6 weeks. IV immunoglobulin therapy was finished when a complete response was observed for at least 8 weeks. The mean duration of IV immunoglobulin was 36.5 months (range 7 to 74 months). Participants were followed up for a minimum of 15 months to a maximum of 87 months (mean 44 months) **Comparators** No comparator	**Critical outcomes** **Disease activity** 2/8 (25%) achieved complete response and 6/8 (75%) achieved partial response mRSSS reduced from 82.38 (37 **to** 145, SD 40.76) to 14.88 (0 to 37, SD 12.99) (p=0.012) PGA scores: 3/8 had full improvement and 5/8 had partial improvement **Systemic involvement/extracutaneous manifestations** All systemic symptoms improved with IV immunoglobulin except arthralgias in 2/8 participants. No statistical analysis reported **Important outcomes** **Duration of clinical improvement or response to treatment** 6/8 (75%) maintenance infusions were needed to maintain disease control. 2/8 (25%) who obtained complete response, stopped treatment after 7 and 11 months but relapses occurred after 6 and 25 months, respectively, and IV immunoglobulin was restarted **Progression to dermatoneuro syndrome** 2/8 (25%) 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]) **Safety** 13 adverse events in 5 people	This study was appraised using the Joanna Briggs Institute checklist for case series 1.Yes 2.Yes 3.Yes 4.Yes 5.Yes 6.Yes 7.Yes 8.Yes 9.Yes 10.Yes Other comments: The study is a case series and, as such, is rated as poor in the hierarchy of study designs. However, there are few eligible participants for studies using new treatments in rare diseases (such as scleromyxedema), meaning it is difficult to conduct high quality studies. Key limitations are that treatment with IV immunoglobulin was open label, there was no comparator, and the sample size was small (n=8). As with many case series, the study was not powered for statistical hypothesis testing and the data should be regarded as descriptive only. Case series have no comparators, and unknown or unmeasured factors may have influenced the findings reported. Case series cannot prove cause and effect and should only be considered hypothesis generating. Source of funding: Not reported

	Mean baseline mRSSS was 82.38 (37-145, SD 40.763)		Adverse event (number of people): asthenia (4), headache (3), exfoliative keratolysis (2), acute hypertensive episodes (1), fever (1), dizziness (1), hypotension (1)	
Full citation Mahevas T, Arnult B, Bouaziz JD et al. (2020) Plasma cell-directed therapies in monoclonal gammopathy-associated scleromyxedema. Blood;135(14) 1101-1110 **Study location** France **Study type** Retrospective case series **Study aim** The aim of the study was to investigate the clinical and therapeutic features of monoclonal gammopathy associated scleromyxedema **Study dates** Between January 1999 and June 2018	**Inclusion criteria** Participants had to have 3 or more of the 4 Rongioletti and Rebora criteria (1: papular eruption, 2: mucin deposition, fibroblast proliferation, fibrosis on skin histology, 3: monoclonal gammopathy, 4: the absence of thyroid disease) **Exclusion Criteria** None reported **Total sample size** 33 people in the entire cohort but only 25 had IV immunoglobulin alone (15 first line, 6 second line, 4 third line). **No. of participants in each treatment group** 25 people had IV immunoglobulin **Baseline characteristics** Baseline characteristics (reported for the entire cohort [n=33] and include people not on IV immunoglobulin alone, outcomes for these people are not reported in this review): • 17 males and 16 females • Mean (SD) age 55.4 years (±13.6) • Mean (SD) age at diagnosis 56.3 years (±13.6, range 28 to 78 years)	**Interventions** IV immunoglobulin first, second, or third line 2 g/kg per month **Comparators** No comparator	**Critical outcomes** **Disease activity** Complete and partial remission 1st line (mean follow up 21 months): 10/15 achieved complete response, 5/15 achieved partial response 2nd line (mean follow up 24 months): 2/6 achieved complete response, 4/6 achieved partial response 3rd line (mean follow up 28 months): 0/4 achieved complete response, 4/4 achieved partial response **Important outcomes** **Progression to dermatoneuro syndrome** 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 **Safety** **Adverse events** 1/15 people who had first line IV immunoglobulin had the severe side effect of thrombosis	This study was appraised using the Joanna Briggs Institute checklist for case series 1.Yes 2.Yes 3.Yes 4.No 5.Yes 6.Yes 7.Yes 8.No 9.Yes 10.No Other comments: The study is a case series and, as such, is rated as poor in the hierarchy of study designs. However, there are few eligible participants for studies using new treatments in rare diseases (such as scleromyxedema), meaning it is difficult to conduct high quality studies. Key limitations are that the study was retrospective, treatment with IV immunoglobulin was open label, there was no comparator, and the sample size was small. As with many case series, the study was not powered for statistical hypothesis testing and the data should be regarded as descriptive only. Case series have no comparators, and unknown or unmeasured factors may have influenced the findings reported. Case series cannot prove cause and effect and should only be considered hypothesis generating. Source of funding: Not reported
Full citation	**Inclusion criteria**	**Interventions**	**Critical outcomes**	This study was appraised using the Joanna Briggs Institute checklist for case series

Mecoli CA., Talbot CC., Fava A et al. (2020) Clinical and molecular phenotyping in scleromyxedema pre- and post- treatment with intravenous immunoglobulin. Arthritis Care and Research, 72(6);761-767. **Study location** Baltimore, Maryland, USA **Study type** Prospective case series **Study aim** The study aimed 'to explore whether IV immunoglobulin would introduce a measurable biologic effect corresponding with clinical improvement'. **Study dates** Not reported	People diagnosed with scleromyxedema with skin involvement. People were either newly diagnosed, treatment naive or undergoing IV immunoglobulin maintenance therapy **Exclusion Criteria** None reported **Total sample size** 15 people **No. of participants in each treatment group** All 15 participants received IV immunoglobulin **Baseline characteristics** 12/15 participants (80%) were female and 3/15 participants (20%) were male Mean age (±SD) 53 years ±11 years 14 participants (93%) were Caucasian 12 participants (80%) were receiving maintenance IV immunoglobulin, and 3 participants (20%) were treatment naïve. The average duration on IV immunoglobulin for the 12 participants on maintenance therapy at baseline was 4.2±2.5 years, and the average number of infusions was 24 The mean PGA score was 1.4±0.2, the mean HAQ-DI score was 0.62±0.7 and the mean MMRSS was 13.6±2.6 The mean body surface area affected was 36±38%	IV immunoglobulin 2 g/kg over a period ranging from 2 to 5 days All participants had IV immunoglobulin infusions every 4 weeks and then the interval increased to every 6 to 12 weeks once their improvement in skin involvement had plateaued **Comparators** No comparator	**Disease activity** Mean PGA scores post treatment reduced from 1.4±0.2 to 1.1±0.2 (p=0.100) Mean body surface area affected post treatment reduced from 36±38% to 25±29% (p=0.099) Mean skin scale pain scores post treatment reduced from 1.8±2.4 to 1.4±2.4 (p=0.252) Mean skin scale flexibility scores (0 to 10) (lower is better) post treatment reduced from 5.4±3.5 to 3.3±3.1 (p=0.013) Mean skin scale softening scores (0 to10) (lower is better) post treatment reduced from 4.9±3.4 to 2.7±2.5 (P=0.022) Mean skin scale global (0 to 10) post treatment reduced from 4.5±3.3 to 2.7±2.4 (p=0.029) Mean MMRSS scores (0 to 60) post treatment reduced from 13.6±2.6 to 10.3±1.9 (p=0.003) The second data collection point was approximately 1 to 2 weeks after IV immunoglobulin was completed **Health related quality of life** Mean HAQ-DI scores post treatment reduced from 0.62±0.7 to 0.54±0.2 (p=0.403)	1.Yes 2.Yes 3.Yes 4.Yes 5.Yes 6.Yes 7.Yes 8.Yes 9.Yes 10.Yes Other comments: The study is a case series and, as such, is rated as poor in the hierarchy of study designs. However, there are few eligible participants for studies using new treatments in rare diseases (such as scleromyxedema), meaning it is difficult to conduct high quality studies. Key limitations are that treatment with IV IMMUNOGLOBULIN was open label, there was no comparator, and the sample size was small (n=15). As with many case series, the study was not powered for statistical hypothesis testing and the data should be regarded as descriptive only. Case series have no comparators, and unknown or unmeasured factors may have influenced the findings reported. Case series cannot prove cause and effect and should only be considered hypothesis generating. Source of funding: Not reported

	The mean skin scale pain score was 1.8±2.4, the mean skin scale flexibility was 5.4±3.5, the mean skin scale softening was 4.9±3.4 and the mean skin scale global was 4.5±3.3 No adjuvant therapy was taken by participants during the study			
Full citation Rongioletti F, Merlo G, Cinotti E et al (2013) Scleromyxedema: a multicenter study of characteristics, comorbidities, course, and therapy in 30 patients. J Am Acad Dermatol, 69(1):66-72. **Study location** Multi-centre Europe **Study type** Retrospective case series **Study aim** 'To describe the characteristics of patients with scleromyxedema regarding demographics, clinical characteristics, comorbidities, therapeutic interventions, and course.' **Study dates** January 2000 to April 2012	**Inclusion criteria** People diagnosed with scleromyxedema with the following criteria (1: generalised papular and sclerodermoid eruption, 2: mucin deposition, fibroblast proliferation, and fibrosis, 3: monoclonal gammopathy, 4: the absence of thyroid disease) **Exclusion Criteria** None reported **Total sample size** 30 people in the entire cohort but only 11 had IV immunoglobulin alone within a treatment period (6 first,2 second line, 2 third line, and one fifth line) **No. of participants in each treatment group** 11 people had IV immunoglobulin **Baseline characteristics** Baseline characteristics (reported for the entire cohort [n=30] and include people not on IV immunoglobulin alone, outcomes for these people are not reported in this review): • 17 males and 13 females • Mean age 59 years (range 34 to 86)	**Intervention** 'Usually' IV immunoglobulin 2 g/kg per month 6 people had IV immunoglobulin alone 1st line 2 people had IV immunoglobulin 2nd line (after prednisone) 2 people had IV immunoglobulin 3rd line (one person after prednisolone, followed by photopheresis; one person after methotrexate, followed by prednisone) One person had IV immunoglobulin 5th line (after cyclosporine, followed by azathioprine, followed by cyclophosphamide, followed by methotrexate and prednisone) **Comparison** No comparator	**Critical outcomes** **Disease activity** 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	This study was appraised using the Joanna Briggs Institute checklist for case series 1.Yes 2.Yes 3.Yes 4.No 5.Yes 6.Yes 7.Yes 8.No 9.Yes 10.No Other comments: The study is a case series and, as such, is rated as poor in the hierarchy of study designs. However, there are few eligible participants for studies using new treatments in rare diseases (such as scleromyxedema), meaning it is difficult to conduct high quality studies. Key limitations are that the study was retrospective, treatment with IV immunoglobulin was open label, there was no comparator, and the sample size was small. As with many case series, the study was not powered for statistical hypothesis testing and the data should be regarded as descriptive only. Case series have no comparators, and unknown or unmeasured factors may have influenced the findings reported. Case series

	Mean duration of scleromyxedema at diagnosis 9 months (range 1 to 60)			cannot prove cause and effect and should only be considered hypothesis generating. Source of funding: None

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

Appendix F Quality appraisal checklists

Joanna Briggs Institute Critical Appraisal Checklist for Case Series

1. Were there clear criteria for inclusion in the case series?
2. Was the condition measured in a standard, reliable way for all participants included in the case series
3. Were valid methods used for the identification of the condition for all participants included in the case series?
4. Did the case series have consecutive inclusion of participants?
5. Did the case series have complete inclusion of participants?
6. Was there clear reporting of the demographics of the participants in the study?
7. Was there clear reporting of clinical information of the participants?
8. Were the outcomes or follow up results of cases clearly reported?
9. Was there clear reporting of the presenting site(s)/clinic(s) demographic information?
10. Was statistical analysis appropriate?

Appendix G GRADE profiles

Table 2: Question: In people with scleromyxedema, what is the clinical effectiveness and safety of human normal immunoglobulin as monotherapy or in addition to current standard care compared to standard care?

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					Score		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Pre IV immunoglobulin treatment	Post IV immunoglobulin treatment	Result		
Disease activity (4 case series)									
Complete response, mean 33.5 months									
Case series Rongioletti et al. (2013)	Very serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	-	-	First line: 3/6 Second line: 0/2 Third line: 0/2 Fifth line: 0/1	Critical	Very Low
Complete response[A], mean 44 months									
Case series Guarneri et al. (2017)	Serious limitations[3]	Serious indirectness[2]	Not applicable	Not calculable	-	-	2/8 (25%)	Critical	Very Low
Complete response, mean 4.3 years									
Case series Mahevas et al. (2020)	Very serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	-	-	First line: 10/15 Second line: 2/6 Third line: 0/4	Critical	Very Low
Partial response, mean 33.5 months									
Case series Rongioletti et al. (2013)	Very serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	-	-	First line: 3/6 Second line: 2/2 Third line: 2/2 Fifth line: 1/1	Critical	Very Low
Partial response[B], mean 44 months									

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					Score		Effect		
Study	**Risk of bias**	**Indirectness**	**Inconsistency**	**Imprecision**	**Pre IV immunoglobulin treatment**	**Post IV immunoglobulin treatment**	**Result**		
Case series Guarneri et al. (2017)	Serious limitations[3]	Serious indirectness[2]	Not applicable	Not calculable	-	-	6/8 (75%)	Critical	Very Low
Partial response, mean 4.3 years									
Case series Mahevas et al. (2020)	Very serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	-	-	First line: 5/15 Second line: 4/6 Third line: 4/4	Critical	Very Low
mRSSS[C], mean 44 months (Mean score, range 0 to 182; a lower score indicates beneficial result)									
Case series Guarneri et al. (2017)	Serious limitations[3]	Serious indirectness[2]	Not applicable	Not calculable	82.38±40.76	14.88±12.99	p=0.012	Critical	Very low
MMRSS, 1 to 2 weeks after IV immunoglobulin (Mean score, range 0 to 60; a lower score indicates beneficial result)									
Case series Mecoli et al (2020)	Serious limitations[3]	Serious indirectness[2]	Not applicable	Not calculable	13.6±2.6	10.3±1.9	p=0.003	Critical	Very low
Physician's global assessment, mean 44 months (measured on a scale of 0 to 2, where 0 = no improvement, 1= partial improvement, 2 = full improvement)									
Case series Guarneri et al. (2017)	Serious limitations[3]	Serious indirectness[2]	Not applicable	Not calculable			5/8 scored 1 3/8 scored 2	Critical	Very low
Physicians global assessment, 1 to 2 weeks after IV immunoglobulin (Mean; measured on a scale of −4 to +4, where +4 = markedly improved, 0 = no change, and −4 = markedly worse)									
Case series Mecoli et al (2020)	Serious limitations[3]	Serious indirectness[2]	Not applicable	Not calculable	1.4±0.2	1.1±0.2	p=0.100	Critical	Very low
Body surface area, 1 to 2 weeks after IV immunoglobulin (Mean [%]; a lower score indicates beneficial result)									

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					Score		Effect		
Study	**Risk of bias**	**Indirectness**	**Inconsistency**	**Imprecision**	**Pre IV immunoglobulin treatment**	**Post IV immunoglobulin treatment**	**Result**		
Case series Mecoli et al (2020)	Serious limitations[3]	Serious indirectness[2]	Not applicable	Not calculable	36±38%	25±29%	p=0.099	Critical	Very low
Skin pain scores, 1 to 2 weeks after IV immunoglobulin (Mean; a lower score indicates beneficial result)									
Case series Mecoli et al (2020)	Serious limitations[3]	Serious indirectness[2]	Not applicable	Not calculable	1.8±2.4	1.4±2.4	p=0.252	Critical	Very low
Skin scale flexibility scores, 1 to 2 weeks after IV immunoglobulin (Mean; range 0 to 10; a lower score indicates beneficial result)									
Case series Mecoli et al (2020)	Serious limitations[3]	Serious indirectness[2]	Not applicable	Not calculable	5.4±3.5	3.3±3.1	p=0.013	Critical	Very low
Skin scale softening scores, 1 to 2 weeks after IV immunoglobulin (Mean; range 0 to 10; a lower score indicates beneficial result)									
Case series Mecoli et al (2020)	Serious limitations[3]	Serious indirectness[2]	Not applicable	Not calculable	4.9±3.4	2.7±2.5	p=0.022	Critical	Very low
Skin scale global, 1 to 2 weeks after IV immunoglobulin (Mean; range 0 to 10; a lower score indicates beneficial result)									
Case series Mecoli et al (2020)	Serious limitations[3]	Serious indirectness[2]	Not applicable	Not calculable	4.5±3.3	2.7±2.4	p=0.029	Critical	Very low
Systemic involvement/extracutaneous manifestations (1 case series)									
Systemic symptoms, mean 44 months									
Case series Guarneri et al. (2017)	Serious limitations[3]	Serious indirectness[2]	Not applicable	Not calculable			All systemic symptoms improved with IV immunoglobulin except arthralgias in 2/8 participants	Critical	Very Low
Health related quality of life (1 case series)									
Health related quality of life, 1 to 2 weeks after IV immunoglobulin (Mean HAQ-DI; a lower score indicates beneficial result)									

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					Score		Effect		
Study	**Risk of bias**	**Indirectness**	**Inconsistency**	**Imprecision**	**Pre IV immunoglobulin treatment**	**Post IV immunoglobulin treatment**	**Result**		
Case series Mecoli et al (2020)	Serious limitations[3]	Serious indirectness[2]	Not applicable	Not calculable	0.62±0.7	0.54±0.2	p=0.403	Critical	Very low
Duration of clinical improvement or response to treatment (1 case series)									
Number of people who needed maintenance treatment with IV immunoglobulin, mean 44 months									
Case series Guarneri et al. (2017)	Serious limitations[3]	Serious indirectness[2]	Not applicable	Not calculable	-	-	6/8 (75%)	Important	Very Low
Number of people who had a relapse on IV immunoglobulin treatment, mean 44 months									
Case series Guarneri et al. (2017)	Serious limitations[3]	Serious indirectness[2]	Not applicable	Not calculable	-	-	2/8 (25%) who obtained 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	Important	Very Low
Progression to dermatoneuro syndrome (2 case series)									
Progression to dermatoneuro syndrome, mean 44 months									
Case series Guarneri et al. (2017)	Serious limitations[3]	Serious indirectness[2]	Not applicable	Not calculable	-	-	2/8 (25%)	Important	Very Low
Progression to dermatoneuro syndrome, cardiac injury, or death, mean 21 months (first line) and 24 months (second line)									
Case series	Very serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	-	-	First line: 4/15	Important	Very Low

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					Score		Effect		
Study	**Risk of bias**	**Indirectness**	**Inconsistency**	**Imprecision**	**Pre IV immunoglobulin treatment**	**Post IV immunoglobulin treatment**	**Result**		
Mahevas et al. (2020)							Second line: 1/6		
Safety (2 case series)									
Adverse events, mean 44 months									
Case series Guarneri et al. (2017)	Serious limitations[3]	Serious indirectness[2]	Not applicable	Not calculable			13 adverse events in 5 people Adverse event (number of people): asthenia (4), headache (3), exfoliative keratolysis (2), acute hypertensive episodes (1), fever (1), dizziness (1), hypotension (1)	Important	Very Low
Severe side effects, mean 21 months									
Case series Mahevas et al. (2020)	Very serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	-	-	1/15 people had thrombosis	Important	Very Low

Abbreviations

HAQ-DI, health assessment questionnaire disability index; IV, intravenous; mRSSS, modified Rodnan skin score; MMRSS, modification of the modified Rodnan Skin Score

A Where complete response was defined as no symptoms
B Where partial response was defined as a decrease in skin changes and improvement in systemic symptoms
C Modified Rodnan skin score determined by these clinical features in 20 different body districts: skin thickening; papular involvement; erythema/dyspigmentation

1 Small numbers of participants were included in the study, retrospective study design with poor outcome reporting
2 Case series
3 Small numbers of participants were included in the study

Glossary

Arthralgias.	Discomfort, pain, or inflammation arising from any part of a joint including cartilage, bone, ligaments, tendons or muscles
Human normal immunoglobulin	Human normal immunoglobulin is used in a variety of conditions, many of which involve the immune system and reduce or stop antibody production. It is prepared using donated human plasma and contains immunoglobulin G (IgG) and antibodies to various viruses. It is generally given intravenously or subcutaneously.
Scleromyxedema	Scleromyxedema (scleromyxoedema) is an extremely rare condition involving pathological deposits of mucin in the skin and connective tissue.

References

Included studies

- Guarneri A, Cioni M, Rongioletti F (2017) High-dose intravenous immunoglobulin therapy for scleromyxedema: a prospective open-label clinical trial using an objective score for clinical evaluation system. JEADV 32, 1157-1160
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