NICE advice

Skin involvement in systemic sclerosis: rituximab

Evidence summary
Published: 7 March 2017

www.nice.org.uk/guidance/es7

Key points

The content of this evidence summary was up-to-date in March 2017. See summaries of product characteristics (SPC), British national formulary (BNF) or the MHRA or NICE websites for up-to-date information.

Regulatory status: Rituximab (MabThera, Roche Products Limited) is a monoclonal antibody. Rituximab is licensed in adults for treating non-Hodgkin's lymphoma, chronic lymphocytic leukaemia, rheumatoid arthritis, and granulomatosis with polyangiitis and microscopic polyangiitis. It is administered as an intravenous infusion. Rituximab is not licensed for treating systemic sclerosis (or localised scleroderma) and use for this indication is off-label.

Overview

This evidence summary includes 7 studies that investigated rituximab (usually 375 mg/m^2 weekly for 4 weeks at 0 and 6 months, or 1,000 mg at 0 and 2 weeks) for treating skin

involvement in systemic sclerosis (mainly diffuse). Most were open-label observational studies without a comparator. In 6 of the 7 studies, compared with baseline, statistically significant improvements were seen with rituximab at follow-ups of 6 months to 4 years in:

- skin thickening (modified Rodnan skin scores [mRSS])
- functional impairment (Health Assessment Questionnaire Disability Index [HAQ-DI] scores)
- disease activity and severity (European Scleroderma Study Group [EScSG] index scores).

The improvements in skin thickening and functional impairment often reached the level considered to be the minimum clinically important amount. In the 2 studies that compared rituximab and usual care directly, rituximab was better than usual care at improving skin thickening, with a statistically significant difference between the groups at most time points. No statistically significant improvement in skin thickening was seen in the seventh study.

Although the studies included in this evidence summary suggest that rituximab may be effective for treating skin involvement in some people with diffuse systemic sclerosis, the evidence is of low quality and has many limitations, and it is difficult to draw any firm conclusions from it. The studies included small numbers of participants (total n=177) and most were open-label, observational studies without a comparator, making it difficult to determine whether any improvements seen with rituximab were related to the treatment or not. In the majority of the studies, there was no blinding of treatment or outcome assessment. Also, participants in many studies were receiving concomitant immunosuppressants and it cannot be excluded that these contributed to any improvement in symptoms. The study populations varied and it is unclear which people might benefit most from treatment, which dosage is optimal and how often treatment cycles need to be repeated.

The adverse effects seen in the studies reflect those listed in the SPC for rituximab. Several deaths and hospitalisations were reported with rituximab (and usual care): not all were considered related to the study medication.

Specialists involved in producing this evidence summary considered that rituximab should be used only for treating skin involvement in diffuse systemic sclerosis that is refractory to standard treatments, after all other options (such as autologous stem cell transplantation),

have been explored, and taking into account the risk of serious adverse effects.

A summary to inform local decision-making is shown in table 1.

Table 1 Summary of the evidence on effectiveness, safety, patient factors and resource implications

Effectiveness

- Statistically significant improvements in **skin thickening** (mRSS) from baseline were seen with rituximab in 5 studies (Daoussis et al. 2010, Daoussis et al. 2016, Jordan et al. 2015, Bosello et al. 2015 and Melsens et al. 2016) and 1 follow-up study (Daoussis et al. 2012) at follow-ups of 6 months to 4 years: no significant improvement was seen in the 7th study (Lafyatis et al. 2009).
- At follow-ups of 6 months to 4 years, in the 3 studies with a comparator, no statistically significant improvements in skin thickening from baseline were seen with usual care in Daoussis et al. (2010) or Jordan et al. (2015), but a significant improvement was seen with usual care in Daoussis et al. (2016).
- Rituximab was statistically significantly better than usual care at improving skin thickening at 1, 2 and 3 years, but not at 4 years in Daoussis et al. (2016) and at 6 months in Jordan et al. (2015).
- Daoussis et al. (2010) found a statistically significant improvement in **functional impairment** (HAQ-DI) from baseline to 1 year with rituximab, but not with usual care. The improvement with rituximab continued at 2 years in Daoussis et al. (2012). Improvements were also found from baseline to 1–4 years with rituximab in Bosello et al. (2015), (statistically significant) and Lafyatis et al. (2009) (no statistical analysis).
- Bosello et al. (2015) found statistically significant improvements in **disease activity and severity** (EScSG indices) from baseline to 4 years with rituximab, and Melsens et al. (2016) found a statistically significant improvement in disease activity from baseline to 12 months.

Safety

- Noting that not all studies had a usual care group, 7 deaths occurred in people receiving rituximab, of which at least 2 were considered unrelated to study treatment, and 2 deaths occurred in people receiving usual care. Five people receiving rituximab were reportedly hospitalised, compared with 10 people receiving usual care, although the number is likely to be higher because only 2 studies provided this information.
- Overall, the adverse effects seen in the studies reflect those listed in the SPC for rituximab. The most commonly reported adverse effects were respiratory tract, urinary tract and other infections, infusion-related reactions, fatigue, rigors and nausea.
- Serious adverse events reported in 1 or 2 participants included hepatitis B virus reactivation, and cardiac and renal adverse events.

Patient factors

- Rituximab is administered by intravenous infusion.
- It is generally given in addition to other treatments for scleroderma, including other immunosuppressants.
- Premedication with paracetamol, an antihistamine and methylprednisolone is required to reduce the risk of adverse effects.
- Skin thickening may improve spontaneously, without treatment.

Resource implications

- Rituximab 10 mg/ml concentrate for solution for intravenous infusion costs £349.25 for 2×10 ml vials and £873.15 for 1×50 ml vial (MIMS, January 2017).
- A cycle of rituximab 375 mg/m^2 weekly for 4 weeks at 0 and 6 months costs £9,779.20 (for a dose of 700 mg) assuming body surface area is 1.86 m^2.
- A cycle of rituximab 1,000 mg at 0 and 2 weeks costs £3,492.60.
- These costs are for the medicine only and do not include VAT, any local procurement discounts or other costs incurred, such as dilution and administration or standard supportive therapy.

Introduction and current guidance

Scleroderma is an autoimmune condition that affects the skin, internal organs and blood vessels, causing scarring and thickening of the tissue in these areas. There are 2 main types of scleroderma: localised scleroderma and systemic sclerosis. Localised scleroderma is confined to the skin and underlying tissues (NHS Choices: scleroderma). Systemic sclerosis can involve internal organs, causing them to become hard and fibrous and function less efficiently (Scleroderma & Raynaud's UK: Systemic sclerosis factsheet).

There are 2 types of systemic sclerosis: limited cutaneous systemic sclerosis and diffuse cutaneous systemic sclerosis. Limited cutaneous systemic sclerosis tends to progress more slowly than diffuse cutaneous disease, although it can be associated with complications such as pulmonary hypertension. It often starts as Raynaud's phenomenon, and other symptoms include thickening of the skin over the extremities and face, red spots (dilated blood vessels) on the skin and hard lumps of calcium underneath the skin (especially the fingertips). In diffuse cutaneous systemic sclerosis, skin changes can affect the whole body. Symptoms tend to come on suddenly and get worse quickly over the first few years; then the disease settles and skin may improve. The gastrointestinal tract, heart, lungs or kidneys can be affected causing a range of symptoms such as diarrhoea or constipation, shortness of breath, high blood pressure and pulmonary hypertension (NHS Choices: scleroderma).

The aim of treatment in scleroderma is to relieve symptoms, prevent the disease getting worse, detect and treat any complications, and minimise disability through occupational

therapy and physiotherapy. Because scleroderma can affect many different parts of the body, various different medicines may be needed (NHS Choices: scleroderma).

The British Society for Rheumatology (BSR) and British Health Professionals in Rheumatology (BHPR) published a guideline for treating systemic sclerosis in 2016 (NICE accredited). These advise that:

- People with early diffuse cutaneous systemic sclerosis should be offered an immunosuppressant (methotrexate, mycophenolate [see the evidence summary on mycophenolate for scleroderma] or cyclophosphamide), although the evidence base is weak.
- Some people might later be candidates for autologous hematopoietic stem cell transplant.
- Skin involvement may be treated with either methotrexate or mycophenolate. Other options include cyclophosphamide, oral corticosteroid therapy (in as low a dose as possible to suppress symptoms, and with close monitoring of renal function) and possibly rituximab. Azathioprine or mycophenolate should be considered after cyclophosphamide to maintain improvement in skin sclerosis and/or lung function.

None of the immunosuppressants recommended for consideration in the BSR/BHPR guideline are licensed for use in people with scleroderma and use of any of these medicines would be off-label.

NHS England is developing a clinical commissioning policy on Rituximab for connective tissue disease with interstitial lung disease. This evidence summary considers rituximab for treating skin involvement in systemic sclerosis: evidence for rituximab for treating lung involvement in systemic sclerosis is not discussed.

Product overview

Mode of action

Rituximab (MabThera, Roche Products Limited) is a monoclonal antibody that targets the CD20 surface antigen, which is expressed on normal and malignant B cells. Rituximab binds to the CD20 surface antigen on B cells mediating cell lysis and inducing cell death by apoptosis (summary of product characteristics).

Regulatory status

Rituximab concentrate for solution for intravenous infusion (MabThera, Roche Products Limited) is licensed in adults for treating non-Hodgkin's lymphoma, chronic lymphocytic leukaemia, rheumatoid arthritis, and granulomatosis with polyangiitis and microscopic polyangiitis. It is administered as an intravenous infusion.

Rituximab is also available as a solution for subcutaneous injection (MabThera, Roche Products Limited), which is licensed for non-Hodgkin's lymphoma. This evidence summary does not consider this formulation of rituximab.

Rituximab is not licensed for treating systemic sclerosis (or localised scleroderma) and use for this indication is off-label.

In line with the guidance from the General Medical Council (GMC) on prescribing unlicensed medicines, the prescriber should take full responsibility for determining the needs of the person and whether using rituximab is suitable outside its authorised indications. Supporting information and advice is also available from the GMC.

Dosing information

Dosing information varies for rituximab depending on the indication it is being used for. The recommended dose is 375 mg/m^2 body surface area for non-Hodgkin's lymphoma and granulomatosis with polyangiitis and microscopic polyangiitis, and 500 mg/m^2 for chronic lymphocytic leukaemia (after 1 dose of 375 mg/m^2). The recommended treatment intervals and durations differ across these conditions. For rheumatoid arthritis, the recommended dosage is 2×1,000 mg doses of rituximab administered 2 weeks apart, with dosing repeated at no less than 6-month intervals. More information on dosage regimens for the licensed indications can be found in the summary of product characteristics.

Dosing information for rituximab for systemic sclerosis (an off-label indication) is discussed in the evidence review within this evidence summary.

Cost

Rituximab 10 mg/ml concentrate for solution for intravenous infusion costs £349.25 for 2×10 ml vials and £873.15 for 1×50 ml vial (excluding VAT; MIMS, January 2017).

Evidence review

A literature search was conducted which identified 17 references (see search strategy for full details). These references were screened using their titles and abstracts and 13 references were obtained and assessed for relevance.

Of these references, 7 were included in this evidence summary:

- 1 open-label randomised controlled trial (RCT) (Daoussis et al. 2010) and an associated follow-up study (Daoussis et al. 2012)
- 1 open-label non-randomised comparative study (Daoussis et al. 2016)
- 1 retrospective nested case-control study (Jordan et al. 2015)
- 3 prospective open-label non-comparative observational studies (Bosello et al. 2015, Lafyatis et al. 2009 and Melsens et al. 2016).

A summary of the included studies is shown in table 2 (see evidence tables for full details). Only evidence relating to skin involvement in systemic sclerosis is discussed in the evidence summary because NHS England is developing a clinical commissioning policy on Rituximab for connective tissue disease with interstitial lung disease.

Table 2 Summary of included studies

Study	Population	Intervention and comparison	Primary outcomes
Daoussis et al. (2010) Single centre prospective open-label RCT Plus Daoussis et al. (2012) Follow-up study	14 people with diffuse SSc and ILD	8 participants born on an even-numbered date received rituximab 375 mg/m^2 weekly for 4 weeks at baseline and at 6 months in addition to their usual treatment 6 participants born on an odd-numbered date received their usual treatment only	Changes in lung function tests and mRSS

Daoussis et al. (2016) Multicentre prospective open-label non-randomised comparative study	51 people with SSc-associated ILD	33 participants chose to receive rituximab 375 mg/m^2 weekly for 4 weeks at baseline, repeated 6 monthly for at least 2 cycles (with or without other immunosuppressants) 18 participants declined rituximab and received conventional treatment only	Changes in lung function tests and mRSS
Jordan et al. (2015) Multicentre, retrospective nested case-control study	63 people with SSc who had been treated with rituximab	Several dosage regimens were used. 75% of participants received 2 infusions of rituximab 1,000 mg 2 weeks apart 25 of the rituximab participants with severe diffuse disease were matched with controls from the EUSTAR database who had not been treated with rituximab	Change in mRSS
Bosello et al. (2015) Open-label, prospective non-comparative study	20 people with progressive, diffuse cutaneous SSc	2 infusions of rituximab 1,000 mg 2 weeks apart No comparator	Changes in mRSS and lung function tests
Lafyatis et al. (2009) Open-label, prospective non-comparative study	15 people with early diffuse cutaneous SSc	2 infusions of rituximab 1,000 mg 2 weeks apart No comparator	Change in mRSS

Melsens et al. (2016) Open-label, prospective non-comparative study	14 people with early diffuse cutaneous SSc	2 infusions of rituximab 1,000 mg 2 weeks apart at 0 and 6 months No comparator	Sensitivity to change of the EScSG activity index
Abbreviations: EScSG, European Scleroderma Study Group; EUSTAR, European Scleroderma Trial and Research; ILD, interstitial lung disease; mRSS, modified Rodnan skin score; RCT, randomised controlled trial; SSc, systemic sclerosis			

The remaining 6 references were excluded. These are listed in excluded studies with reasons for their exclusion.

Clinical effectiveness

An overview of the study results for clinical effectiveness can be found in the results tables.

Skin thickness: modified Rodnan skin score (mRSS)

In the open-label RCT by Daoussis et al. (2010), in people with diffuse systemic sclerosis and interstitial lung disease receiving rituximab (n=8), a statistically significant improvement was seen in skin thickness (assessed using the modified Rodnan skin score [mRSS]) at 1 year compared with baseline (mean improvement 5.13, p=0.0003). The improvement was within the range considered to include the minimum clinically important value (range 3 to 7.5 [Gazi H et al. 2007]). By comparison, no statistically significant difference from baseline was seen in participants receiving usual care (n=6).

The median percentage improvement in mRSS from baseline to 1 year was 39.25% in the rituximab group compared with 20.80% in the usual care group; however, the difference between the groups did not reach statistical significance (p=0.06). Daoussis et al. (2010) noted that this might be because of the small number of participants in the study and the short period between biopsies (24 weeks).

The uncontrolled follow-up study by Daoussis et al. (2012) found that, at 2 years, mRSS had improved further in the participants who received rituximab in Daoussis et al. (2010)

compared with baseline (mean improvement 8.63, which is considered clinically important, p<0.0001). The median percentage improvement in mRSS from baseline increased to 64.58% at 2 years (no statistical analysis).

In their open-label non-randomised comparative study in people with systemic sclerosis and interstitial lung disease, Daoussis et al. (2016), found statistically significant improvements from baseline in mRSS with rituximab (n=33) at all time points (1, 2, 3 and 4 years, mean improvements 5.89 to 10.19, all p<0.01, all clinically important). Statistically significant improvements from baseline were also seen with usual care (n=18) at 2, 3 and 4 years (mean improvements 2.25 to 4.14, all p<0.05), but not 1 year.

Daoussis et al. (2016) compared the 2 groups and found that rituximab was better than usual care at improving mRSS at 1, 2 and 3 years (differences 3.89, 4.88 and 7.94 respectively; p=0.002, p=0.015 and p=0.002) but not at 4 years. The differences between the groups at 1–3 years were statistically significant and within or above the range considered to include the minimum clinically important value.

In their retrospective nested case-control study in 25 people with severe, diffuse systemic sclerosis, Jordan et al. (2015) found a statistically significant improvement in mRSS from baseline in the rituximab group at 6 months (mean improvement 6.3, which is clinically important, p=0.0001). No statistically significant difference from baseline was seen in the control group. The difference in mRSS between rituximab and control was 4.4, which was statistically significant (p=0.02) and within the range considered to include the minimum clinically important value.

The nested case-control analysis also found a statistically significant improvement in the median percentage improvement in mRSS from baseline to 6 months in the rituximab group compared with the usual care group (24.0% compared with 7.7% respectively, p=0.03).

In addition to the network analysis, Jordan et al. (2015) prospectively looked at mean changes in mRSS in 46 people with systemic sclerosis and a subgroup of these who had diffuse disease (n=35). They found statistically significant improvements from baseline with rituximab in both groups, which were within the range considered to include the minimum clinically important value (mean improvements 3.7 and 4.4 respectively, p=0.0002 and p=0.0005 respectively).

Three prospective open-label non-comparative observational studies have assessed the

effects of rituximab in diffuse cutaneous systemic sclerosis: Bosello et al. (2015) (n=20) in progressive disease and Lafyatis et al. (2009) (n=15) and Melsens et al. (2016) (n=14) in early disease (less than 18 months and less than 4 years respectively).

Bosello et al. (2015) found statistically significant improvements in mRSS from baseline with rituximab at all time points (all $p<0.0001$ except 6 months, $p=0.001$). The mean improvements from 6 months to 4 years ranged from 7.9 to 14.2, which are above the values considered clinically important.

Melsens et al. (2016) also found statistically significant improvements in mRSS from baseline with rituximab at all time points (all $p<0.001$). The score improved over time from baseline to 12 months: the mean improvement was 5.9 at 3 months and 14.4 at 12 months.

The study by Lafyatis et al. (2009), which had a 12-month follow-up, was the only study included in this evidence summary which found no statistically significant changes in mRSS from baseline with rituximab.

See the results tables for more details.

Functional disability: Health Assessment Questionnaire Disability Index (HAQ-DI)

In their open-label RCT in people with diffuse systemic sclerosis and interstitial lung disease, Daoussis et al. (2010) found a statistically significant improvement in functional impairment (assessed using the HAQ-DI) at 1 year in participants receiving rituximab (n=8), compared with baseline (median improvement 0.38, $p=0.03$). The improvement was above the range considered to include the minimum clinically important value (range 0.2 to 0.25 [Gazi H et al. 2007]). No statistically significant difference from baseline was seen in participants receiving usual care (n=6). It is not reported whether there was any significant difference between rituximab and usual care.

In the rituximab group in Daoussis et al. (2010), functional impairment improved in 6 participants (shown by an improvement in HAQ-DI of more than 0.2) and was unchanged in 2 participants over 1 year. By comparison, in the usual care group, 3 participants improved, 2 were unchanged and 1 participant got worse.

The uncontrolled follow-up study by Daoussis et al. (2012) found that, at 2 years, HAQ-DI had continued to improve in the participants receiving rituximab compared with baseline

(median improvement 0.44, which is considered clinically important, p<0.0001).

In the prospective open-label non-comparative study in people with diffuse cutaneous systemic sclerosis by Bosello et al. (2015) (n=20), statistically significant improvements in HAQ-DI from baseline were seen with rituximab at all time points (all p<0.0001). The mean improvement remained consistent at 0.5 to 0.6 (clinically important) over a mean follow-up of 48.5 months.

Small improvements in HAQ-DI were seen in people with early (less than 18 months) diffuse cutaneous systemic sclerosis in the prospective open-label non-comparative study by Lafyatis et al. (2009) (n=15); however, these did not reach the level considered to be clinically important (mean improvement 0.03 at 6 months and 0.12 at 12 months). The statistical significance of the improvements was not reported.

HAQ-DI was not assessed in the studies by Daoussis et al. (2016), Jordan et al. (2015) or Melsens et al. (2016).

See the results tables for more details.

Disease activity and severity: European Scleroderma Study Group (EScSG) indices

In their prospective open-label non-comparative study in people with diffuse cutaneous systemic sclerosis (n=20), Bosello et al. (2015) found that statistically significant improvements in disease activity (assessed by the EScSG index) from baseline were seen with rituximab at all time points (all p<0.0001). The mean improvement remained consistent at 4.0 to 4.3 over a mean follow-up of 48.5 months. It is unclear whether this improvement is clinically important.

Statistically significant improvements from baseline were also seen in the EScSG severity index at all time points (all p<0.0001) in the study by Bosello et al. (2015). The mean severity improved over time from baseline to 4 years. The mean improvement was 3.4 at the last available follow-up; however, the clinical importance of this is uncertain.

A steady improvement in the EScSG disease activity index was seen in people with early (less than 4 years) diffuse cutaneous systemic sclerosis in the prospective open-label non-comparative study by Melsens et al. (2016) (n=14). The improvement from baseline was statistically significant at all time points (all p<0.001) and at 12 months reached 3.6.

The minimum clinically important treatment effect is unclear for the EScSG indices.

EScSG disease activity and severity indices were not assessed in the studies by Daoussis et al. (2010), Daoussis et al. (2012), Daoussis et al. (2016), Jordan et al. (2015) or Lafyatis et al. (2009).

See the results tables for more details.

Safety and tolerability

Several deaths were reported in the studies included in the evidence summary. In the open-label non-randomised comparative study by Daoussis et al. (2016), 5/33 participants (15%) receiving rituximab died (3 with end-stage lung fibrosis, 1 with lung cancer, and 1 with sudden death of unknown cause) compared with 2/18 (11%) receiving usual care (both with respiratory tract infections: no statistically significant difference between the groups). Two deaths were reported in the study by Bosello et al. (2015) (1 with heart failure and 1 with arrhythmia), which were considered probably unrelated to study medicines.

Adverse events were reported in all of the studies but the severity of adverse events is not always clear. In the open-label RCT and follow-up study by Daoussis et al. (2010) and Daoussis et al. (2012), 2/8 participants in the rituximab group were hospitalised (with respiratory tract infections) and 1 experienced a mild infusion reaction, whereas 0/6 participants in the usual care group reported adverse events (no statistical analysis). In Daoussis et al. (2016), 3/33 participants (9%) receiving rituximab were hospitalised (with respiratory or urinary infections) compared with 10/18 (56%) receiving usual care (9 with respiratory or urinary tract infections and 1 with digital ulcers: no statistical analysis).

Overall, the adverse effects seen in the studies reflect those listed in the summary of product characteristics for rituximab. The most commonly reported adverse effects were respiratory tract, urinary tract and other infections (sometimes leading to hospitalisation), infusion-related reactions (generally mild), fatigue, rigors and nausea. Serious adverse events reported in 1 or 2 participants included hepatitis B virus reactivation, and cardiac and renal adverse events. An overview of the study results for safety and tolerability can be found in the results tables.

According to the summary of product characteristics, signs and symptoms suggestive of an infusion-related reaction have been reported in more than 50% of participants in clinical

trials across rituximab's licensed indications, with 12% of participants experiencing severe reactions. Severe infusion-related reactions with a fatal outcome have been reported in post-marketing use. Premedication with an antipyretic and an antihistamine should be given before administration of intravenous rituximab. In addition, premedication with a glucocorticoid should be given (except in people with non-Hodgkin's lymphoma or chronic lymphocytic leukaemia who are receiving rituximab in combination with glucocorticoid-containing chemotherapy).

Very rare cases of fatal progressive multifocal leukoencephalopathy have been reported after use of rituximab and people should be monitored at regular intervals for any new or worsening neurological symptoms or signs suggestive of this condition.

Serious infections, including fatalities can occur during rituximab therapy, and rituximab is contraindicated in people with an active, severe infection (for example, tuberculosis, sepsis and opportunistic infections), and in people who are severely immunocompromised. In addition, cases of hepatitis B reactivation, including those with a fatal outcome, have been reported in people receiving rituximab. Hepatitis B virus screening should be performed in all people before starting treatment with rituximab and people with active hepatitis B infection should not be treated with this medicine.

Severe skin infections, such as toxic epidermal necrolysis and Stevens–Johnson syndrome (some with fatal outcome), have been reported in people receiving rituximab. Treatment with rituximab should be stopped if such an event occurs.

See the summary of product characteristics for rituximab for full details of warnings, contraindications and adverse events.

Evidence strengths and limitations

The studies included in the evidence summary have many limitations that affect their application to clinical practice. All included small numbers of participants and most were open-label, observational studies without a comparator (Bosello et al. 2015, Lafyatis et al. 2009 and Melsens et al. 2016). Observational studies are particularly susceptible to bias, confounding and other methodological problems, and these studies cannot prove that systemic sclerosis improved because of rituximab: they can only suggest that rituximab was associated with an improvement in the condition.

In the majority of the studies, there was no blinding of treatment or outcome assessment.

Also, participants in many studies were receiving concomitant immunosuppressants and it cannot be excluded that these contributed to any improvement in symptoms. Similarly, many participants received concomitant pre-treatment with methylprednisolone. It is important to note that, many of the improvements seen in mRSS were of borderline clinical importance only. Nevertheless, results are based on the whole cohort and it is possible that some individual participants will have seen clinically important improvements.

In the studies where a comparator was used, the method of treatment allocation was not ideal and allocation concealment was not reported. The comparative study by Daoussis et al. (2016) was not randomised: participants chose whether to receive rituximab or usual care. In addition, the treatment and control groups were heterogeneous in terms of disease duration. In the study by Daoussis et al. (2010) participants were randomised according to their date of birth, which led to unbalanced numbers in each group. Also, this study included only 14 participants and was not sufficiently statistically powered to reliably detect any differences between the groups.

The nested case-control analysis by Jordan et al. (2015) has some further limitations. For example, it is a multicentre study and, although this means it reflects clinical experience in Europe, there may be differences in ratings of outcomes across investigators and centres. Some data were collected retrospectively, which could lead to recall bias.

Skin thickening often improves spontaneously during the natural course of scleroderma, making it difficult to determine whether any improvements seen with rituximab are related to the treatment or not, particularly in people with longstanding disease. Daoussis et al. (2012), noted that the median percentage improvement seen in their study (n=8) was 40% and that this is higher than the 20% expected during the natural course of the disease. For comparison, Jordan et al. (2015) found that the median percentage improvement in mRSS from baseline to 6 months in the rituximab group was 24.0% compared with 7.7% in the usual care group in their nested case-control analysis (n=25), with a statistically significant difference between the groups (p=0.03).

Participants in the comparative studies had longstanding scleroderma (average duration around 6 to 8 years) and had previously received a variety of immunosuppressants. They may have had disease that was resistant to treatment, which was more likely to deteriorate over the course of the study, or they may have been at a stage in the disease where spontaneous resolution was likely. Overall, the studies mostly included people with diffuse systemic sclerosis, but some of the study populations were heterogeneous in terms of disease duration, severity and previous treatments.

Although benefits in terms of skin thickening, functional impairment and disease activity and severity were seen in the majority of the studies, these limitations should be taken into account. The study populations varied and it is unclear which people might benefit most from treatment. Also, several different dosage regimens were used (primarily 375 mg/m^2 weekly for 4 weeks at baseline and 6 months, and 1,000 mg at 0 and 2 weeks); therefore, it is unclear which dosage is optimal and how often treatment cycles need to be repeated.

An overview of the quality assessment of each included study can be found in the evidence tables.

Estimated impact for the NHS

Other medicines

The British Society for Rheumatology (BSR) and British Health Professionals in Rheumatology (BHPR) guideline for treating systemic sclerosis advises that skin involvement in diffuse systemic sclerosis may be treated with either methotrexate or mycophenolate. Other options include cyclophosphamide, oral corticosteroid therapy and possibly rituximab. Azathioprine or mycophenolate should be considered after cyclophosphamide to maintain improvement in skin sclerosis and/or lung function. Use of any of these immunosuppressants would be off-label.

Costs of other medicines

No cost-effectiveness studies of rituximab for treating scleroderma were identified.

Table 3 shows the cost of rituximab alongside the costs of other immunosuppressants that are used for diffuse systemic sclerosis; however, these costs are not directly comparable for many reasons. Although the BSR/BHPR guideline advises which immunosuppressants may be considered, they do not make any recommendations around dosage or duration. Dosages for rituximab included in the table are those commonly used in the studies: dosages for other immunosuppressants are based on the summaries of product characteristics for other indications and expert opinion. The doses shown do not represent the full range that can be used and they do not imply therapeutic equivalence. Note that, in the studies, rituximab was used in addition to other, conventional immunosuppressants, not instead of these medicines.

The costs shown in the table are for the medicines only (excluding VAT) and do not include any local procurement discounts or other costs incurred, such as dilution and administration, standard supportive therapy, or attendance for day case treatment. They also assume that vials are used for only 1 patient and are not shared between patients. Standard supportive therapy for rituximab includes premedication with paracetamol, an antihistamine and methylprednisolone.

Table 3 Costs of rituximab compared with other immunosuppressants

Medicine	Usual dose[a]	Estimated annual cost excluding VAT
Rituximab (intravenous)	375 mg/m^2 weekly for 4 weeks at baseline and 6 months	£9,779.20[b,c]
	1,000 mg at 0 and 2 weeks	£3,492.60[c,d]
Methotrexate (oral)	15 mg weekly	£19.72[e]
Cyclophosphamide (intravenous)	15 mg/kg monthly	£204.72[f]
Cyclophosphamide (oral)	2 mg/kg daily	£1,522.05[g]
Mycophenolate mofetil (oral)	1,000 mg twice daily	£180.16[h]
Mycophenolate sodium (oral)	720 mg twice daily	£2,353.40[c]
Azathioprine (oral)	2.5 mg/kg daily	£64.85[i]

[a] Dosages for rituximab are those commonly used in the studies. Dosages for other medicines are based on the summaries of product characteristics for other indications and expert opinion. None of these medicines are licensed for scleroderma and use would be off-label. The doses shown do not represent the full range that can be used and they do not imply therapeutic equivalence

[b] Based on a dose of 700 mg for an adult with a body surface area of 1.86 m^2 given 1×50 ml and 2×10 ml vials for each dose

[c] Cost taken from MIMS, January 2017

[d] Assuming no further treatment cycles; some participants in the studies received more than 1 cycle of treatment

[e] Cost taken from the Drug Tariff, January 2017

[f] Cost taken from the British national formulary (BNF), January 2017; based on a 70 kg adult given 1×1 g vial monthly

[g] Cost taken from the Drug Tariff, January 2017; based on a 70 kg adult given 3×50 mg tablets daily

[h] Cost taken from the Drug Tariff, January 2017; based on 500 mg tablets: 250 mg capsules would be substantially more expensive at £2,401.99

[i] Costs taken from the Drug Tariff, January 2017; based on a 70 kg adult given 1×25 mg and 3×50 mg tablets daily

Current or estimated usage

Estimating current usage of rituximab for treating scleroderma is difficult because rituximab is used to treat various conditions. No information on prescribing rituximab for scleroderma was available at the time this evidence summary was prepared.

Likely place in therapy

Local decision makers need to take safety, efficacy, cost and patient factors into account when considering the likely place in therapy of rituximab for systemic sclerosis.

The BSR/BHPR guideline for treating systemic sclerosis suggests that methotrexate and mycophenolate are the preferred options for treating skin involvement in diffuse systemic sclerosis. Cyclophosphamide and oral corticosteroid therapy (in as low a dose as possible to suppress symptoms, and with close monitoring of renal function) are other options, and

rituximab is listed as a possible option. Although the studies included in this evidence summary suggest that rituximab may be effective for treating skin involvement in some people with diffuse systemic sclerosis, the evidence is of low quality and has many limitations, and it is difficult to draw any firm conclusions from it.

The adverse effects seen in the studies reflect those listed in the summary of product characteristics for rituximab. Several deaths and hospitalisations were reported with rituximab (and usual care): not all were considered related to the study medication.

The acquisition cost of rituximab is more than that of other medicines that are used for diffuse systemic sclerosis. However, many factors need taking into account. In the studies, rituximab was often taken in addition to other immunosuppressants.

Specialists involved in producing this evidence summary considered that rituximab is currently only an option for treating skin involvement in diffuse systemic sclerosis that is progressing despite an adequate trial of standard immunosuppressant treatment (or when standard immunosuppressant treatment cannot be tolerated) in limited situations. For example, when autologous hematopoietic stem cell transplantation is contraindicated, or when cyclophosphamide is not suitable because of the risk of sterility and there are no other options. The risk of serious adverse effects with rituximab should be taken into account.

Information for the public about medicines

Evidence summaries provide an overview of the best evidence that is available about specific medicines. They also give general information about the condition that the medicine might be prescribed for, how the medicine is used, how it works, and what the aim of treatment is.

Evidence summaries aim to help healthcare professionals and patients decide whether medicines are safe to use and if they are likely to work well, especially when there isn't another suitable medicine that has a licence for the condition. They don't contain recommendations from NICE on whether the medicine should be used.

Information about licensing of medicines

In the UK, medicines need to have a licence before they can be widely used. To get a licence, the manufacturer of the medicine has to provide evidence that shows that the medicine works well enough and is safe enough to be used for a specific condition and for a specific group of patients, and that they can manufacture the medicine to the required quality. Evidence summaries explain whether a medicine has a licence, and if it does what the licence covers.

There is more information about licensing of medicines on NHS Choices.

Medicines can be prescribed if they don't have a licence (unlicensed) or for 'off-label' use. Off-label means that the person prescribing the medicine wants to use it in a different way than that stated in its licence. This could mean using the medicine for a different condition or a different group of patients, or it could mean a change in the dose or that the medicine is taken in a different way. If a healthcare professional wants to prescribe an unlicensed medicine, or a licensed medicine off-label, they must follow their professional guide, for example for doctors the General Medical Council's good practice guidelines. These include giving information about the treatment and discussing the possible benefits and harms so that the person has enough information to decide whether or not to have the treatment. This is called giving informed consent.

Questions that might be useful to ask about medicines

- Why am I being offered this medicine?
- Why am I being offered a medicine that is unlicensed or is being used off-label?
- What does the treatment involve?
- What are the benefits I might get?
- How good are my chances of getting those benefits?
- Could having the treatment make me feel worse?
- Are there other treatments I could try?

- What are the risks of the treatment?
- Are the risks minor or serious? How likely are they to happen?
- What could happen if I don't have the treatment?

NICE guidance and advice

NICE has published several technology appraisals relating to licensed indications for the intravenous formulation of rituximab. The use of rituximab for scleroderma is not appropriate for referral for a NICE technology appraisal and is not currently planned into any other work programme.

NICE has not issued any clinical guidelines on managing scleroderma but has published the following advice relating to this condition:

- scleroderma: oral mycophenolate
- digital ulcers: sildenafil

References

Bosello SL, De Luca G, Rucco M et al. (2015) Long-term efficacy of B cell depletion therapy on lung and skin involvement in diffuse systemic sclerosis. Seminars in Arthritis and Rheumatism 44: 428–36

Daoussis D, Liossis SC, Tsamandas AC et al. (2010) Experience with rituximab in scleroderma: results from a 1-year, proof-of-principle study. Rheumatology 49: 271–80

Daoussis D, Liossis SC, Tsamandas AC et al. (2012) Effect of long-term treatment with rituximab on pulmonary function and skin fibrosis in patients with diffuse systemic sclerosis. Clinical and Experimental Rheumatology 30 (Suppl 71): S17–22

Daoussis D, Melissaropoulos K, Sakellaropoulos G et al. (2016) A multicenter, open-label, comparative study of B-cell depletion therapy with rituximab for systemic sclerosis-associated interstitial lung disease. Seminars in Arthritis and Rheumatism

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Jordan S, Distler JHW, Maurer B et al. (2015) Effects and safety of rituximab in systemic sclerosis: an analysis from the European Scleroderma Trial and Research (EUSTAR) group. Annals of the Rheumatic Diseases 74: 1188–94

Lafyatis R, Kissin E, York M et al. (2009) B cell depletion with rituximab in patients with diffuse cutaneous systemic sclerosis. Arthritis and Rheumatism 60: 578–83

Melsens K, De Keyser F, Decuman S et al. (2016) Assessment of sensitivity to change of the European Scleroderma Study Group activity index. Clinical and Experimental Rheumatology 34 (Suppl 100): 148–51

Redelmeier DA and Lorig K (1993) Assessing the clinical importance of symptomatic improvements. Archives of Internal Medicine 153:1337–42

Evidence tables

Table 4 Daoussis et al. (2010) (and follow-up study Daoussis et al. 2012)

Study reference	Daoussis D, Liossis SC, Tsamandas AC et al. (2010) Experience with rituximab in scleroderma: results from a 1-year, proof-of-principle study. Rheumatology 49: 271–80 Daoussis D, Liossis SC, Tsamandas AC et al. (2012) Effect of long-term treatment with rituximab on pulmonary function and skin fibrosis in patients with diffuse systemic sclerosis. Clinical and Experimental Rheumatology 30 (Suppl 71): S17–22
Unique identifier	Not reported
Study type	Open-label RCT and 1-year non-comparative follow-up study

Aim of the study	To investigate the efficacy of rituximab for systemic sclerosis
Study dates	Not reported
Setting	A single centre in Greece
Number of participants	14 participants
Population	People with systemic sclerosis (mean duration 7–8 years). All had diffuse disease
Inclusion criteria	Participants fulfilled the ACR classification criteria for systemic sclerosis. All had ILD and had been on stable treatment in the 12 months before enrolment
Exclusion criteria	Not reported
Intervention(s)	Participants born on an even-numbered date (n=8, median age 53 years, mean mRSS 13.5) received of rituximab 375 mg/m^2 weekly for 4 weeks at baseline and 6 months in addition to their usual treatment[a]
Comparator(s)	Participants born on an odd-numbered date (n=6, median age 56 years, mean mRSS 11.5) received their usual treatment only[a]
Length of follow-up	All participants were followed up for 1 year The 8 participants who received rituximab subsequently received a further 2 cycles of rituximab (at 12 months and 18 months) and were followed for a second year in an uncontrolled follow-up study
Outcomes	Primary outcomes: • Changes in lung function tests • Changes in mRSS

	Secondary outcomes: • Changes in skin histology • Changes on lung imaging • Changes in functional impairment using the 20-item HAQ-DI	
	Safety outcomes: • Adverse effects	
Source of funding	The Hellenic Rheumatology Society. Also, Roche Hellas paid the open access publication charges	
Overall risk of bias/quality assessment (CASP RCT checklist)	Did the trial address a clearly focused issue?	Yes
	Was the assignment of participants to treatments randomised?	Yes[b]
	Were participants, health workers and study personnel blinded?	No[c]
	Were the groups similar at the start of the trial?	Yes[d]
	Aside from the experimental intervention, were the groups treated equally?	Yes
	Were all of the participants who entered the trial properly accounted for at its conclusion?	Yes
	How large was the treatment effect?	See table 10
	How precise was the estimate of the treatment effect?	See table 10
	Can the results be applied in your context? (or to the local population)	Yes
	Were all clinically important outcomes considered?	Yes
	Are the benefits worth the harms and costs?	See key points

Study limitations	• The study included only 14 participants and was not sufficiently powered to reliably detect any differences between the groups • The participants in the study were heterogeneous in terms of disease duration, severity and previous treatments • Skin thickening often improves during the natural course of scleroderma • The participants had longstanding disease and had previously received a variety of immunosuppressants. They were receiving concomitant immunosuppressants and it cannot be excluded that these contributed to any improvement in symptoms	
Comments	[a] Generally prednisolone and/or other immunosuppressants. No changes in medication were allowed during the study [b] Participants were randomised to treatment; however, the simple method of randomisation used led to unequal numbers in the groups. Allocation concealment was not reported and may not have been adequate [c] The study was open-label. Assessment of mRSS and lung imaging was blinded [d] The method of randomisation may have led to imbalances in between the groups that could affect response to treatment; however, no significant differences were seen in the baseline characteristics that were reported (including mRSS: 13.5 in the rituximab group compared with 11.5 in the placebo group)	
Abbreviations	ACR, American College of Rheumatology; HAQ-DI, Health Assessment Questionnaire Disability Index; ILD, interstitial lung disease; mRSS, modified Rodnan skin score; RCT, randomised controlled trial	

Table 5 Daoussis et al. (2016)

Study reference	Daoussis D, Melissaropoulos K, Sakellaropoulos G et al. (2016) A multicenter, open-label, comparative study of B-cell depletion therapy with Rituximab for systemic sclerosis-associated interstitial lung disease. Seminars in Arthritis and Rheumatism
Unique identifier	Not reported
Study type	Open-label non-randomised comparative study
Aim of the study	To assess the long-term efficacy and safety of rituximab in ILD associated with systemic sclerosis compared with conventional treatment
Study dates	Not reported
Setting	4 centres in Greece
Number of participants	51 participants
Population	People with ILD associated with systemic sclerosis. 86% had diffuse disease
Inclusion criteria	Participants fulfilled the ACR classification criteria for systemic sclerosis. All had ILD (according to imaging, lung function tests or both) and had been on stable treatment in the 12 months before enrolment
Exclusion criteria	Not reported
Intervention(s)	33 participants (mean age 54 years, mean disease duration 5.7 years, mean mRSS 14.7) chose to receive rituximab 375 mg/m^2 weekly for 4 weeks at baseline, repeated 6 monthly for at least 2 cycles (with or without conventional treatment[a]) 19 participants received at least 4 cycles of rituximab and completed a 2-year follow-up
Comparator(s)	18 participants (mean age 52 years, mean disease duration 2.6 years, mean mRSS 17.8) declined rituximab and received conventional treatment only[a]

Length of follow-up	Maximum follow-up was 7 years. Median follow-up was 4 years	
Outcomes	Primary outcomes: • Changes in lung function tests • Changes in mRSS	
	Safety outcomes: • Adverse effects	
Source of funding	Partially funded by a 'Karathodori' grant	
Overall risk of bias/quality assessment (CASP RCT checklist)	Did the trial address a clearly focused issue?	Yes
	Was the assignment of participants to treatments randomised?	No
	Were participants, health workers and study personnel blinded?	No[b]
	Were the groups similar at the start of the trial?	No[c]
	Aside from the experimental intervention, were the groups treated equally?	Yes
	Were all of the participants who entered the trial properly accounted for at its conclusion?	Yes
	How large was the treatment effect?	See table 11
	How precise was the estimate of the treatment effect?	See table 11
	Can the results be applied in your context? (or to the local population)	Yes
	Were all clinically important outcomes considered?	Yes

	Are the benefits worth the harms and costs?	See key points
Study limitations	• The study was not designed to reliably detect any differences between the groups • The treatment and control groups were heterogeneous in terms of disease duration • Participants were receiving concomitant immunosuppressants and it cannot be excluded that these contributed to any improvement in symptoms	
Comments	[a] Prednisolone and/or other immunosuppressants [b] The study was open-label. It is not reported whether outcome assessors were blind or not, but this is probably unlikely [c] Baseline characteristics were usually similar between the groups, but disease duration was statistically significantly shorter in the control group (2.6 years compared with 5.7 years in the rituximab group, p=0.012). It is unclear how this difference might affect the results. The difference in baseline mRSS between the groups was 3, although this was not statistically significant	
Abbreviations	ACR, American College of Rheumatology; FVC, forced vital capacity; ILD, interstitial lung disease; mRSS, modified Rodnan skin score	

Table 6 Jordan et al. (2015)

Study reference	Jordan S, Distler JHW, Maurer B et al. (2015) Effects and safety of rituximab in systemic sclerosis: an analysis from the European Scleroderma Trial and Research (EUSTAR) group. Annals of the Rheumatic Diseases 74: 1188–94
Unique identifier	Not reported

Study type	A prospective observational study including a retrospective nested case-control study
Aim of the study	To analyse the effects of rituximab on skin and lung fibrosis and safety in people in the EUSTAR cohort
Study dates	Not reported
Setting	42 centres in Europe
Number of participants	63 participants (mean age 51 years) treated with rituximab 25 participants with severe diffuse systemic sclerosis (mRSS ≥16/51) were matched with controls
Population	People with systemic sclerosis (median duration 6 years, 35/63 with diffuse disease, average mRSS 18.1) who were prospectively included in the EUSTAR database and treated with rituximab at the discretion of their doctor
Inclusion criteria	Inclusion criteria were fulfilment of ACR classification criteria for systemic sclerosis, treatment with rituximab, and at least 1 follow-up
Exclusion criteria	People were excluded if they had autologous stem cell transplantation between baseline and follow-up
Intervention(s)	• 47 participants received 2 infusions of rituximab 1,000 mg 2 weeks apart • 13 participants received 1 infusion of rituximab 1,000 mg • 3 participants received other dosage regimens • 31 participants also received concomitant methylprednisolone 100 mg with rituximab • 41 participants also received conventional treatment with 1 or more immunosuppressants (including prednisolone) or colchicine

Comparator(s)	The control group included people in the EUSTAR database with systemic sclerosis (according to the same criteria) who were not treated with rituximab, and had at least 1 follow-up Matching criteria included mRSS, FVC, follow-up duration, scleroderma subtype, disease duration and concomitant immunosuppressant treatment	
Length of follow-up	Data were collected over a 6-month period. Median follow up was 7 months (IQR 4 to 9 months)	
Outcomes	Primary outcome: • difference between the groups in change in mRSS from baseline to follow-up in the nested case-control cohort	
	Secondary outcomes: • difference between the groups in change in FVC from baseline to follow-up in participants with evidence of ILD • changes from baseline in mRSS in the whole cohort and in participants with diffuse disease	
	Safety outcomes: • Adverse effects	
Source of funding	None	
Overall risk of bias/quality assessment (CASP case-control study checklist)	Did the study address a clearly focused issue?	Yes
	Did the authors use an appropriate method to answer their question?	Yes[a]
	Were the cases recruited in an acceptable way?	Yes[b]
	Were the controls selected in an acceptable way?	Yes
	Was the exposure accurately measured to minimise bias?	Unclear[c]
	What confounding factors have the authors accounted for?	See comments[d]

	Have the authors taken account of the potential confounding factors in the design and/or in their analysis?	Yes
	What are the results of this study?	See table 12
	How precise are the results? (How precise is the estimate of risk?)	See table 12
	Do you believe the results?	Yes
	Can the results be applied to the local population?	Yes
	Do the results of this study fit with other available evidence?	Yes
Study limitations	• Observational studies are prone to bias, confounding and other methodological problems, and can only show association, not causation • The nested analysis included a relatively small number of participants and it is unclear if it was sufficiently powered • It is unclear whether all potential confounders were considered • There may be differences in rating of mRSS across investigators and centres • Most data were collected prospectively, but some were collected retrospectively, which could lead to recall bias • Skin thickening often improves during the natural course of scleroderma • Many participants received concomitant treatment with methylprednisolone, which may have affected symptoms. Similarly, most also received other immunosuppressants	

Comments	[a] An RCT would have been preferable; however, a nested case-control study is a suitable option to test a hypothesis in a rare condition [b] As is usual for this type of study, there may be selection bias because doctors chose which participants were treated with rituximab [c] EUSTAR investigators are trained to assess mRSS, and consistent and appropriate outcomes are recorded across the EUSTAR cohort; however, investigators were not blinded [d] The cases and controls in the nested analysis were matched for potential confounders relating to severity and duration of disease, and concomitant treatment. Baseline characteristics were generally similar between the groups, although there was a statistically significant difference in baseline mRSS between the groups in the nested case-control analysis (rituximab 26.6 compared with control 25.0, p=0.03)
Abbreviations: ACR, American College of Rheumatology; EUSTAR, European Scleroderma Trial and Research; FVC, forced vital capacity; ILD, interstitial lung disease; IQR, inter quartile range; mRSS, modified Rodnan skin score; RCT, randomised controlled trial	

Table 7 Bosello et al. (2015)

Study reference	Bosello SL, De Luca G, Rucco M et al. (2015) Long-term efficacy of B cell depletion therapy on lung and skin involvement in diffuse systemic sclerosis. Seminars in Arthritis and Rheumatism 44: 428–36
Unique identifier	Not reported
Study type	Open-label, prospective non-comparative study
Aim of the study	To evaluate the safety and efficacy of long-term rituximab in people with diffuse systemic sclerosis
Study dates	Not reported
Setting	A single centre in Italy
Number of participants	20 participants (mean age 23 years)

Population	People with progressive, diffuse systemic sclerosis (mean duration 30 months, mean mRSS 22.3)[a]
Inclusion criteria	Participants fulfilled the ACR classification criteria for systemic sclerosis
Exclusion criteria	Exclusion criteria were rest dyspnoea or signs and symptoms of heart failure, infections, immunodeficiency or a history of tuberculosis contact, or cancer
Intervention(s)	All participants received 2 infusions of rituximab 1,000 mg 2 weeks apart. Methylprednisolone 100 mg was co-administered with each infusion[b]. Only 1 participant also received a conventional immunosuppressant
Comparator(s)	None
Length of follow-up	Mean follow-up was 48.5 months
Outcomes	Primary outcomes: • Changes in mRSS • Changes in lung function tests and lung imaging
	Secondary outcomes: • Changes in functional impairment using the HAQ-DI • Changes in EScSG disease activity and severity indices
	Safety outcomes: • Adverse effects
Source of funding	The ASRALES Foundation and GILS
Overall risk of bias/quality assessment	Quality assessment checklist not completed. See evidence strengths and limitations for more information.

Study limitations	• Observational study subject to bias and confounding • Small number of participants • No comparator • No blinding of treatment or outcome assessment, although mRSS was assessed by 2 independent observers • It is unclear if the EScSG indices have been validated
Comments	[a] 13 participants (65%) had early disease (<3 years since Raynaud's phenomenon occurred). In 18 participants (80%), skin scores had worsened by >10% after cyclophosphamide treatment [b] During follow-up, 8 participants were retreated with further cycles of rituximab because skin scores worsened by >10% (n=4) or arthritis flares occurred (n=4)
Abbreviations	ACR, American College of Rheumatology; EScSG, European Scleroderma Study Group (disease activity and severity indices); HAQ-DI, Health Assessment Questionnaire Disability Index; mRSS, modified Rodnan skin score

Table 8 Lafyatis et al. (2009)

Study reference	Lafyatis R, Kissin E, York M et al. (2009) B cell depletion with rituximab in patients with diffuse cutaneous systemic sclerosis. Arthritis and Rheumatism 60: 578–83
Unique identifier	Not reported
Study type	Open-label, prospective non-comparative study
Aim of the study	To assess the efficacy of rituximab in diffuse cutaneous systemic sclerosis, examine potential mechanisms of action, and investigate supplementary outcome measures for trials in systemic sclerosis
Study dates	Not reported
Setting	A single centre in the USA

Number of participants	15 participants (mean age 46 years)
Population	People with early[a], diffuse cutaneous systemic sclerosis (mean duration 14.5 months, mean mRSS 20.6)
Inclusion criteria	Participants fulfilled the ACR classification criteria for systemic sclerosis
Exclusion criteria	People were usually excluded if they were receiving conventional immunosuppressants (including prednisolone 10 mg daily or more). However, 1 participant had methotrexate. Other exclusion criteria were FVC or diffusion capacity <50% of the predicted, significant cardiac arrhythmia or ejection fraction <40%
Intervention(s)	All participants received 2 infusions of rituximab 1,000 mg 2 weeks apart
Comparator(s)	None
Length of follow-up	Outcomes were assessed at 6 and 12 months
Outcomes	Primary outcome: • Changes in mRSS
	Secondary outcomes: • Changes in lung function tests and lung imaging • Changes in functional impairment using the HAQ-DI • Changes in various pathological skin outcomes
	Safety outcomes: • Adverse effects
Source of funding	Genentech and Biogen Idec, and NIH grants

Overall risk of bias/quality assessment	Quality assessment checklist not completed. See evidence strengths and limitations for more information.
Study limitations	• Observational study subject to bias and confounding • Small number of participants • No comparator • No blinding of treatment or outcome assessment, although mRSS was assessed by 2 trained doctors
Comments	[a] Early disease was defined as non-Raynaud's phenomenon occurring with 18 months of trial entry
Abbreviations	ACR, American College of Rheumatology; FVC, forced vital capacity; HAQ-DI, Health Assessment Questionnaire Disability Index; mRSS, modified Rodnan skin score

Table 9 Melsens et al. (2016)

Study reference	Melsens K, De Keyser F, Decuman S et al. (2016) Assessment of sensitivity to change of the European Scleroderma Study Group activity index. Clinical and Experimental Rheumatology 34 (Suppl 100): 148–51
Unique identifier	NCT00379431
Study type	Open-label, prospective non-comparative study
Aim of the study	To assess sensitivity to change of the EScSG disease activity index in people with early, severe diffuse cutaneous systemic sclerosis treated with rituximab
Study dates	Not reported
Setting	A single centre in Belgium
Number of participants	14 participants (median age 52 years)

Population	People with early[a], diffuse cutaneous systemic sclerosis (mean duration 10 months, mean mRSS 24.8)
Inclusion criteria	Participants fulfilled the ACR classification criteria for systemic sclerosis. Other inclusion criteria were age >18 years, early[a] disease, mRSS ≥14, and EScSG activity score ≥3
Exclusion criteria	Exclusion criteria were FVC ≤ 50% of predicted, diffusion capacity ≤40% of the predicted value, left ventricular ejection fraction ≤40%, serious or uncontrolled co-existing diseases, infection, immunodeficiency and a history of cancer
Intervention(s)	All participants received 2 infusions of rituximab 1,000 mg 2 weeks apart, with methylprednisolone 100 mg Prednisolone ≤10mg/day was allowed. Other immunosuppressants were replaced with methotrexate 15 mg weekly (unless contraindicated)
Comparator(s)	None
Length of follow-up	Follow-up was 12 months
Outcomes	Primary outcome: • Changes in EScSG disease activity index
	Secondary outcomes: • Changes in mRSS • Changes in lung function tests and echocardiography
	Safety outcomes: • Adverse effects
Source of funding	Research Foundation, Flanders
Overall risk of bias/quality assessment	Quality assessment checklist not completed. See evidence strengths and limitations for more information.

Study limitations	• Observational study subject to bias and confounding • Small number of participants • No comparator • No blinding of treatment or outcome assessment • It is unclear if the EScSG indices have been validated
Comments	[a] Early disease was defined as disease duration ≤4 years since the occurrence of non-Raynaud's phenomenon
Abbreviations	ACR, American College of Rheumatology; EScSG, European Scleroderma Study Group (disease activity and severity indices); FVC, forced vital capacity; mRSS, modified Rodnan skin score

Results tables

Results relating to lung involvement in scleroderma are not discussed in the evidence summary because NHS England is developing a clinical commissioning policy on Rituximab for connective tissue disease with interstitial lung disease.

Table 10 Daoussis et al. (2010) (and follow-up study Daoussis et al. 2012)

	Rituximab	**Usual treatment**	**Analysis**
n=14	**n=8**	**n=6**	
Primary outcome			
Mean change (±SD) in mRSS from baseline to 1 year	Baseline 13.50 (±6.84) • 1 year 8.37 (±6.45 Difference −5.13[a]	Baseline 11.50 (±2.16) • 1 year 9.66 (±3.38 Difference −1.84	Statistically significant improvement from baseline with rituximab (p=0.0003) No statistically significant improvement from baseline with usual care (p=0.16)

Median % change (upper and lower quartiles) in mRSS from baseline to 1 year	−39.25% (−27.33% to −64.95%)	−20.80% (−10.78% to −39.28%)	No statistically significant difference in improvement between the groups (p=0.06)
Selected secondary outcomes			
Median change (upper and lower quartiles) in HAQ-DI from baseline to 1 year	Baseline 0.69 (0.28 to 1.25) • 1 year 0.31 (0.13–0.69 Difference −0.38[b]	Baseline 0.31 (0.09 to 0.90) • 1 year 0.13 (0.09 to 0.40 Difference −0.18	Statistically significant improvement from baseline with rituximab (p=0.03) No statistically significant improvement from baseline with usual care (p=0.130)
Improvement in HAQ-DI of more than 0.2[b]	6/ 8 participants (2 participants saw no change)	3/6 participants (1 participant worsened and 2 participants saw no change)	No statistical analysis
Outcomes reported in follow-up study			
Mean change (±SEM) in mRSS from baseline to 2 years	Baseline 13.50 (±2.42) • 2 years 4.87 (±0.83 Difference −8.63[a]	Not studied past 1 year	Statistically significant improvement from baseline (p<0.0001)
Median % change (upper and lower quartiles) in mRSS from baseline to 2 years	−64.58% (−51.79% to −73.74%)	Not studied past 1 year	No statistical analysis

Median change (upper and lower quartiles) in HAQ-DI from baseline to 2 years	Baseline 0.69 (0.28 to 1.25) • 2 years 0.25 (0.13 to 0.44 Difference −0.44[b]	Not studied past 1 year	Statistically significant improvement from baseline (p<0.0001)
Safety and tolerability outcomes			
n=14	**n=8**	**n=6**	
Number of participants hospitalised	2/8 (25%) (2 with RTI, 1 with associated leukopenia)	None reported	No statistical analysis
Adverse events reported	1 mild infusion reaction	None reported	No statistical analysis
[a] This is within or above the range considered to include the minimum clinically important change in mRSS (3 to 7.5) [b] This is within or above the range considered to include the minimum clinically important change in HAQ-DI (0.2 to 0.25)			
Abbreviations: HAQ-DI, Health Assessment Questionnaire Disability Index; mRSS, modified Rodnan skin score; RTI, respiratory tract infection; SD, standard deviation; SEM, standard error of mean			

Table 11 Daoussis et al. (2016)

	Rituximab	**Usual treatment**	**Analysis**
n=51	**n=33**	**n=18**	
Primary outcome			

Mean changes (±SD) in mRSS from baseline to 4 years	Baseline 14.72 (±10.52) • 1 year 8.83 (±7.83) Difference −5.89[a] • 2 years 5.93 (±5.15) Difference −8.79[a] • 3 years 4.53 (±5.29) Difference −10.19[a] • 4 years 5.37 (±8.34) Difference −9.35[a]	Baseline 17.78 (±9.48) • 1 year 15.78 (±9.89) Difference −2.00 • 2 years 13.72 (±9.67) Difference −4.06[a] • 3 years 15.53 (±9.53) Difference −2.25 • 4 years 13.64 (±8.56) Difference −4.14[a]	Statistically significant improvements from baseline with rituximab at all time points (all p<0.01) Statistically significant improvements from baseline with usual care at 2, 3 and 4 years, but not 1 year (p=0.030, p=0.041, p=0.023 and p=0.064 respectively) Rituximab was statistically significantly better than usual care at 1, 2 and 3 years but not 4 years • 1-year difference 3.89[a] (p= 0.002) • 2-year difference 4.88[a] (p=0.015) • 3-year difference 7.94[a] (p=0.002) • 4-year difference 5.21[a] (p=0.053)
Safety and tolerability outcomes			
N=51	**n=33**	**n=18**	
Number of deaths	5/33 (15%) (3 with end-stage lung fibrosis, 1 with lung cancer, and 1 with sudden death of unknown cause)	2/18 (11%) (both RTI)	No statistically significant difference between the groups (p=0.68)

Number of participants hospitalised	3/33 (9%) (2 with RTI and 1 with UTI)	10/18 (56%) (5 with RTI, 4 with UTI and 1 with digital ulcers)	No statistical analysis
Other adverse effects reported	1 HBV reactivation 2 mild infusion reactions		No statistical analysis
[a] This is within or above the range considered to include the minimum clinically important change in mRSS (3 to 7.5)			
Abbreviations: HBV, hepatitis B virus; mRSS, modified Rodnan skin score; RTI, respiratory tract infection; SD, standard deviation; UTI, urinary tract infection			

Table 12 Jordan et al. (2015)

	Rituximab	**Matched controls**	**Analysis**
n=63	**Whole mRSS cohort[a]: n=46**	**None**	
	Diffuse disease: n=35	**None**	
	Severe, diffuse disease[b] n=25	**n=25**	**Nested case-control analysis**
Primary outcome			
Severe, diffuse disease[b]			

Mean change (±SEM) in mRSS from baseline to 6 months (IQR 5 to 9 months)	Baseline 26.6 (±1.4) • 6 months 20.3 (±1.8) Difference −6.3[c] (±1.4)	Baseline 25.0 (±1.2) • 6 months 23.1 (±1.5) Difference −1.9 (±1.0)	Statistically significant improvement from baseline with rituximab (p=0.0001) No statistically significant improvement from baseline with control (p=0.1) Rituximab was statistically significantly better than control (difference 4.4[c], p=0.02)
Median % change (IQR) in mRSS from baseline to 6 months (IQR 5 to 9 months)	−24.0% (±5.2%)	−7.7% (±4.3%)	Statistically significant improvement from baseline with rituximab (p=0.0001) Statistical significance of improvement from baseline with control not reported Rituximab was statistically significantly better than control (difference 16.3%, p=0.03)
Selected secondary outcomes			
Diffuse disease			
Mean change (±SEM) in mRSS from baseline to 6 months (IQR 3 to 9 months)	Baseline 22.1 (±1.6) • 6 months 17.7 (±1.6 Difference −4.4[c]	Not applicable	Statistically significant improvement from baseline (p=0.0005)
Median % change (IQR) in mRSS from baseline to 6 months (IQR 3 to 9 months)	−16.7% (±5.5%)	Not applicable	Statistically significant improvement from baseline (p=0.005)
Whole cohort			

Mean change (±SEM) in mRSS from baseline to 7 months (IQR 5 to 9 months)	Baseline 18.1 (±1.6) • 7 months 14.4 (±1.5 Difference −3.7[c]	Not applicable	Statistically significant improvement from baseline (p=0.0002)
Median % change (IQR) in mRSS from baseline to 7 months (IQR 5 to 9 months)	−15.0% (±5.3%)	Not applicable	Statistically significant improvement from baseline (p=0.008)
Safety and tolerability outcomes			
n=63[d] (data on adverse events were not reported for the control group)			
Serious adverse events	None reported		
Adverse events reported	1 cardiac/renal involvement 1 arrhythmia 14 fatigue 11 infections 2 nausea 3 rigor 2 serum sickness/hypersensitivity reactions		
[a] Participants with limited or diffuse systemic sclerosis, with mRSS reported at baseline and follow-up [b] The nested case-control analysis was undertaken in the subgroup of participants with mRSS ≥16/51 [c] This is within or above the range considered to include the minimum clinically important change in mRSS (3 to 7.5) [d] The numbers of participants in the analyses for individual adverse effects varied between 48 and 56: the reason for this is unclear			
Abbreviations: IQR, inter quartile range; mRSS, modified Rodnan skin score; SEM, standard error of mean			

Table 13 Bosello et al. (2015)

	Rituximab	Analysis
n=20	**n=20**	
Primary outcome		

Mean changes (±SD) in mRSS from baseline to last available follow-up	Baseline 22.3 (±9.5) • 6 months 14.4 (±8.4) Difference −7.9[a] Median improvement 30.9% (11.1% to 69.2%) • 12 months 11.2 (±7.5) Difference −11.1[a] • 24 months 10.0 (±6.9) Difference −12.3[a] • 36 months 8.1 (±5.2) Difference −14.2[a] • 48 months 9.8 (±7.2) Difference −12.5[a] • Final follow-up[b] 10.8 (±7.2) Difference −11.5[a]	Statistically significant improvement from baseline at all time points (all p<0.0001 except 6 months, p=0.001)
Selected secondary outcomes		

Mean changes (±SD) in HAQ-DI from baseline to last available follow-up	Baseline 1.2 (±0.8) • 6 months 0.7 (±0.8) Difference −0.5[c] • 12 months 0.6 (±0.7) Difference −0.6[c] • Final follow-up[b] 0.6 (±0.9) Difference −0.6[c]	Statistically significant improvement from baseline at all time points (all p<0.0001)
Mean changes (±SD) in EScSG disease activity index from baseline to last available follow-up	Baseline 5.8 (±1.7) • 6 months 1.6 (±1.0) Difference −4.2 • 12 months 1.5 (±1.0) Difference −4.3 • Final follow-up[b] 1.8 (±1.7) Difference −4.0	Statistically significant improvement from baseline at all time points (all p<0.0001)

Mean changes (±SD) in EScSG disease severity index from baseline to last available follow-up	Baseline 10.9 (±3.0) • 6 months 8.0 (±3.0) Difference −2.9 • 12 months 7.7 (±3.0) Difference −3.2 • Final follow-up[b] 7.5 (±3.2) Difference −3.4	Statistically significant improvement from baseline at all time points (all p<0.0001)
Safety and tolerability outcomes		
n=20		
Number of deaths	1 heart failure and 1 arrhythmia (probably unrelated to study medication)	
Number of serious adverse events	1 breast cancer (thought to be unrelated to study medication) and 1 herpes zoster infection	
Adverse events reported	2 ulcer infections 3 URTIs	

[a] This is within or above the range considered to include the minimum clinically important change in mRSS (3 to 7.5)

[b] Final follow-up for each participant; mean follow-up 48.5 months

[c] This is above the range considered to include the minimum clinically important change in HAQ-DI (0.2 to 0.25)

Abbreviations: EScSG, European Scleroderma Study Group (disease activity and severity indices); HAQ-DI, Health Assessment Questionnaire Disability Index; mRSS, modified Rodnan skin score; SD, standard deviation; URTI, upper respiratory tract infection

Table 14 Lafyatis et al. (2009)

	Rituximab	**Analysis**
n=15	**n=15**	
Primary outcome		
Mean changes (±95% CI) in mRSS[a] from baseline to 12 months	Baseline 20.6 (±4.4) • 6 months 20.2 (±5.5) Difference −0.4 (p=0.82) • 12 months 21.1 (±5.2) Difference +0.5 (p=0.83)	No statistically significant changes from baseline at 6 or 12 months (p=0.82 and p=0.83)
Selected secondary outcomes		

Mean changes (±95% CI) in HAQ-DI[b] from baseline to 12 months	Baseline 0.67 (±0.32) • 6 months 0.64 (±0.36) Difference −0.03 • 12 months 0.55 (±0.33) Difference −0.12	No statistical analysis
Safety and tolerability outcomes		
n=15		
Number of serious adverse events	1 prostate cancer (thought to be unrelated to study medication)	
Adverse events reported	7 infusion reactions 2 mild hypotension 1 each of flushing, fatigue, nausea and abdominal cramping, rigors and hand tingling 1 UTI 1 dental abscess	
[a] The minimum clinically important change in mRSS is considered to range from 3 to 7.5 [b] The range considered to include the minimum clinically important change in HAQ-DI is 0.2 to 0.25		
Abbreviations: CI, confidence interval; HAQ-DI, Health Assessment Questionnaire Disability Index; mRSS, modified Rodnan skin score; UTI, urinary tract infection		

Table 15 Melsens et al. (2016)

	Rituximab	Analysis
n=14	**n=14**[a]	
Primary outcome		
Mean changes (±SD) in EScSG disease activity index from baseline to last available follow-up	Baseline 4.3 (±1.8) • 3 months 2.0 (±1.4) Difference −2.3 • 6 months 1.1 (±0.7) Difference −3.2 • 12 months 0.7 (±0.8) Difference −3.6 (95% CI −4.9 to −2.4)	Statistically significant improvement from baseline at all time points (all p<0.001)
Selected secondary outcomes		

Mean changes (±SD) in mRSS from baseline to 12 months	Baseline 24.8 (±4.4) • 3 months 18.9 (±6.3) Difference −5.9[b] • 6 months 14.1 (±4.2) Difference −10.7[b] • 12 months 10.4 (±3.1) Difference −14.4[b] (95% CI −17.3 to −11.6)	Statistically significant improvement from baseline at all time points (all p<0.001)
Safety and tolerability outcomes		
n=14		
Number of deaths	1 sepsis (probably unrelated to study medication)	
Number of serious adverse events	1 CABG, 1 non-infectious subfebrility and 1 renal crisis (all probably unrelated to study medication)	
[a] The 3- and 6-month analyses include only 13 participants because 1 participant died [b] This is within or above the range considered to include the minimum clinically important change in mRSS (3 to 7.5)		
Abbreviations: CABG, coronary artery bypass graft; CI, confidence interval; EScSG, European Scleroderma Study Group (disease activity and severity indices); mRSS, modified Rodnan skin score; SD, standard deviation		

Excluded studies

Study reference	Reason for exclusion
Bosello S, De Santis M, Lama G et al. (2010) B cell depletion in diffuse progressive systemic sclerosis: safety, skin score modification and IL-6 modulation in an up to 36 months follow-up open-label trial. Arthritis Research & Therapy 12: R54	Non-comparative study including less than 10 participants
Fraticelli P, De Vita S, Franzolini N et al. (2015) Reduced type I collagen gene expression by skin fibroblasts of patients with systemic sclerosis after one treatment course with rituximab. Clinical and Experimental Rheumatology 33 (Suppl 91): S160–7	Non-comparative study including less than 10 participants
Phumethum V, Jamal S and Johnson SR (2011) Biologic therapy for systemic sclerosis: a systematic review. The Journal of Rheumatology 38: 289–96	No meta-analyses Provides no additional evidence
Smith V, Van Praet JT, Vandooren B et al. (2010) Rituximab in diffuse cutaneous systemic sclerosis: an open-label clinical and histopathological study. Annals of the Rheumatic Diseases 69: 193–7	Non-comparative study including less than 10 participants
Smith V, Piette Y, van Praet JT et al. (2013) Two-year results of an open pilot study of a 2-treatment course with rituximab in patients with early systemic sclerosis with diffuse skin involvement. The Journal of Rheumatology 40: 52–7	Non-comparative study including less than 10 participants
Smith V, Pizzorni C, Riccieri V et al. (2016) Stabilization of Microcirculation in Patients with Early Systemic Sclerosis with Diffuse Skin Involvement following Rituximab Treatment: An Open-label Study. The Journal of Rheumatology 43: 995–6	Non-comparative study including less than 10 participants

Terms used in this evidence summary

European Scleroderma Study Group disease activity and severity indices

The European Scleroderma Study Group (EScSG) has developed disease activity and severity indices to help assess scleroderma in clinical practice and in clinical trials.

The EScSG disease activity index is a 10-item index with a maximum score of 10, indicating greater disease activity. There are 3 indices: 1 for systemic sclerosis as a whole, 1 for diffuse systemic sclerosis and for limited systemic sclerosis. Items include skin scores, scleroderma, digital necrosis and arthritis on examination; patient-reported deterioration in various symptoms; and several laboratory tests.

The EScSG disease severity index scores 9 organ systems (general, peripheral vascular, skin, joint and tendon, muscle, gastrointestinal tract, lung, heart and kidney) on a scale of 0 to 4, with higher scores indicating worse disease.

The minimal clinically important treatment effect is unclear for the EScSG disease activity and severity indices. It is also unclear if these indices have been validated.

Health Assessment Questionnaire Disability Index

The Health Assessment Questionnaire Disability Index (HAQ-DI) is a validated, self-reported questionnaire with 8 categories (dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activity). Each category includes 2 or 3 questions, which are scored from 0 (without difficulty) to 3 (unable to do). Points may also be added if help and aids or devices are required for usual activities. The score for the disability index is the mean of the 8 category scores and higher scores indicate greater disability.

Redelmeier DA et al. (1993) reported that HAQ-DI scores needed to differ by about 0.19 points for average respondents to stop rating themselves as 'about the same' and start rating themselves as 'somewhat better' (95% confidence interval 0.10 to 0.28). Following a Delphi consensus building exercise, Gazi H et al. (2007) reported that the minimal clinically important treatment effect for the HAQ-DI ranges from 0.2 to 0.25 units.

Modified Rodnan skin score

The modified Rodnan skin score (mRSS) is a validated measure of skin thickness, with

higher scores indicating worse thickening. The skin is palpated in 17 areas (fingers, hands, forearms, arms, feet, legs, thighs, face, chest and abdomen) and scored on a scale of 0–3, where 0 is normal, 1 is mild thickening, 2 is moderate thickening and 3 is severe thickening. The total skin score can range from 0 (no thickening) to 51 (severe thickening in all 17 areas).

Following a Delphi consensus building exercise, Gazi H et al. (2007) reported that, the minimal clinically important treatment effect for the mRSS ranges from 3 to 7.5 units.

Search strategy

Database: Medline

Platform: Ovid

Version: 1946 to November Week 1 2016

Search date: 15th November 2016

Number of results retrieved: 45

Search strategy:

1 Rituximab/ (11512)

2 rituximab.tw. (13753)

3 mabthera.tw. (145)

4 rituxan.tw. (245)

5 reditux.tw. (0)

6 rituxin.tw. (1)

7 c2b8.tw. (66)

8 "idec 102".tw. (0)

9 or/1-8 (16007)

10 scleroderma, localized/ or exp scleroderma, systemic/ (21564)

11 ((Cutaneous or skin or locali?ed or linear or Reynaud*) and (scleroderma or sclerosis or dermatosclerosis or schleroderma or sclerodermia)).tw. (10939)

12 "CREST syndrome".tw. (485)

13 "CRST syndrome".tw. (83)

14 CREST syndrome/ (361)

15 morphea.tw. (994)

16 or/10-15 (27199)

17 9 and 16 (99)

18 Randomized Controlled Trial.pt. (468919)

19 Controlled Clinical Trial.pt. (95017)

20 Clinical Trial.pt. (527305)

21 exp Clinical Trials as Topic/ (322830)

22 Placebos/ (35340)

23 Random Allocation/ (95079)

24 Double-Blind Method/ (147613)

25 Single-Blind Method/ (24504)

26 Cross-Over Studies/ (42542)

27 ((random* or control* or clinical*) adj3 (trial* or stud*)).tw. (937165)

28 (random* adj3 allocat*).tw. (25232)

29 placebo*.tw. (182617)

30 ((singl* or doubl* or trebl* or tripl*) adj (blind* or mask*)).tw. (144509)

31 (crossover* or (cross adj over*)).tw. (67777)

32 or/18-31 (1679657)

33 animals/ not humans/ (4633315)

34 32 not 33 (1563660)

35 Observational Studies as Topic/ (1982)

36 Observational Study/ (29933)

37 Epidemiologic Studies/ (7944)

38 exp Case-Control Studies/ (875337)

39 exp Cohort Studies/ (1711708)

40 Cross-Sectional Studies/ (254408)

41 Controlled Before-After Studies/ (204)

42 Historically Controlled Study/ (86)

43 Interrupted Time Series Analysis/ (256)

44 Comparative Study.pt. (1881171)

45 case control*.tw. (101086)

46 case series.tw. (44147)

47 (cohort adj (study or studies)).tw. (124717)

48 cohort analy*.tw. (5108)

49 (follow up adj (study or studies)).tw. (42331)

50 (observational adj (study or studies)).tw. (60998)

51 longitudinal.tw. (178711)

52 prospective.tw. (424241)

53 retrospective.tw. (335894)

54 cross sectional.tw. (219603)

55 or/35-54 (3966064)

56 34 or 55 (4885965)

57 17 and 56 (47)

58 57 (47)

59 limit 58 to english language (45)

Database: Medline in-process; epubs ahead of print; daily update

Platform: Ovid

Version: 14th November 2016 (all segments)

Search date: 15th November 2016

Number of results retrieved: 14

Search strategy:

1 Rituximab/ (13)

2 rituximab.tw. (2277)

3 mabthera.tw. (14)

4 rituxan.tw. (21)

5 reditux.tw. (0)

6 rituxin.tw. (0)

7 c2b8.tw. (4)

8 "idec 102".tw. (0)

9 or/1-8 (2284)

10 scleroderma, localized/ or exp scleroderma, systemic/ (6)

11 ((Cutaneous or skin or locali?ed or linear or Reynaud*) and (scleroderma or sclerosis or dermatosclerosis or schleroderma or sclerodermia)).tw. (1113)

12 "CREST syndrome".tw. (22)

13 "CRST syndrome".tw. (0)

14 CREST syndrome/ (0)

15 morphea.tw. (130)

16 or/10-15 (1219)

17 9 and 16 (14)

Database: Embase

Platform: Ovid

Version: 1974 to 2016 November 14th

Search date: 15th November 2016

Number of results retrieved: 175

Search strategy:

1 *rituximab/ (15177)

2 rituximab.tw. (30414)

3 mabthera.tw. (1938)

4 rituxan.tw. (2820)

5 reditux.tw. (43)

6 rituxin.tw. (31)

7 c2b8.tw. (131)

8 "idec 102".tw. (1)

9 or/1-8 (34483)

10 exp scleroderma/ (37291)

11 ((Cutaneous or skin or locali?ed or linear or Reynaud*) and (scleroderma or sclerosis or dermatosclerosis or schleroderma or sclerodermia)).tw. (18396)

12 "CREST syndrome".tw. (639)

13 "CRST syndrome".tw. (111)

14 syndrome CREST/ (917)

15 morphea.tw. (1509)

16 morphea/ (1847)

17 or/10-16 (45566)

18 9 and 17 (366)

19 exp Clinical Trials/ (265516)

20 Randomization/ (83378)

21 Placebo/ (326444)

22 Double Blind Procedure/ (137888)

23 Single Blind Procedure/ (27187)

24 Crossover Procedure/ (53801)

25 ((random* or control* or clinical*) adj3 (trial* or stud*)).tw. (1293864)

26 (random* adj3 allocat*).tw. (33821)

27 placebo*.tw. (248731)

28 ((singl* or doubl* or trebl* or tripl*) adj (blind* or mask*)).tw. (196094)

29 (crossover* or (cross adj over*)).tw. (85728)

30 or/19-29 (1741666)

31 nonhuman/ not human/ (3697567)

32 30 not 31 (1683657)

33 Clinical study/ (252506)

34 Case control study/ (122629)

35 Family study/ (27689)

36 Longitudinal study/ (105450)

37 Retrospective study/ (513655)

38 comparative study/ (740593)

39 Prospective study/ (385948)

40 Randomized controlled trials/ (124434)

41 39 not 40 (381226)

42 Cohort analysis/ (300633)

43 cohort analy*.tw. (7780)

44 (Cohort adj (study or studies)).tw. (178783)

45 (Case control* adj (study or studies)).tw. (102954)

46 (follow up adj (study or studies)).tw. (53520)

47 (observational adj (study or studies)).tw. (100810)

48 (epidemiologic* adj (study or studies)).tw. (88909)

49 (cross sectional adj (study or studies)).tw. (131065)

50 case series.tw. (67040)

51 prospective.tw. (626064)

52 retrospective.tw. (572552)

53 or/33-38,41-52 (2964212)

54 32 or 53 (4121131)

55 18 and 54 (182)

56 55 (182)

57 limit 56 to english language (175)

Database: Cochrane Library – incorporating Cochrane Database of Systematic Reviews (CDSR); DARE; CENTRAL; HTA database; NHS EED

Platform: Ovid

Version:

- CDSR – 11 of 12, November 2016
- DARE – 2 of 4, April 2015 (legacy database)
- CENTRAL – 10 of 12, October 2016
- HTA – 4 of 4, October 2016
- NHS EED – 2 of 4, April 2015 (legacy database)

Search date: 14th November 2016

Number of results retrieved: CDSR – 0; DARE – 0; CENTRAL – 8; HTA – 0; NHS EED – 0.

Search strategy:

ID Search

#1 MeSH descriptor: [Rituximab] explode all trees

#2 rituximab:ti,ab

#3 mabthera:ti,ab

#4 rituxan:ti,ab

#5 reditux:ti,ab

#6 rituxin:ti,ab

#7 c2b8:ti,ab

#8 "idec 102":ti,ab

#9 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8

#10 MeSH descriptor: [Scleroderma, Localized] explode all trees

#11 MeSH descriptor: [Scleroderma, Systemic] explode all trees

#12 ((Cutaneous or skin or localised or localized or linear or Reynaud*) and (scleroderma or sclerosis or dermatosclerosis or schleroderma or sclerodermia)):ti,ab

#13 "CREST syndrome":ti,ab

#14 "CRST syndrome":ti,ab

#15 MeSH descriptor: [CREST Syndrome] explode all trees

#16 morphea:ti,ab

#17 #10 or #11 or #12 or #13 or #14 or #15 or #16

#18 #9 and #17

Development of this evidence summary

The evidence summary: process guide (2017) sets out the process NICE uses to select topics for evidence summaries and details how the summaries are developed, quality assured and approved for publication.

Expert advisers

Christopher Denton, Consultant Rheumatologist, University College London Division of Medicine and Royal Free London NHS Foundation Trust.

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Declarations of interest

Christopher Denton undertakes ad hoc personal consultancy in the area of clinical trial design and new potential scleroderma therapy including the following commercial organisations: Actelion, Pfizer, GlaxoSmithKline, Bayer, Sanofi-Aventis, Genentech-Roche, Merck-Serono, CSL Behring and Inventiva.

His department has received research grant funding for work in the area of scleroderma from the following commercial organisations: Actelion, CSL Behring, Inventiva and GlaxoSmithKline.

Ariane Herrick has received research funding from Actelion and has spoken at meetings sponsored by Actelion. Payments were to the University of Manchester, her employer.

Neil McHugh has acted on an advisory board for an educational programme delivered by AbbVie. He has also received grant funding on behalf of his NHS organisation for investigator initiated projects sponsored by Celgene.

About this evidence summary

Evidence summaries provide a summary of the best available published evidence for selected new medicines, unlicensed medicines or off-label use of licensed medicines.

The summaries assess the strengths and weaknesses of the best available evidence to inform health professionals and commissioners' decision-making.

This summary is not NICE guidance.

ISBN: 978-1-4731-2376-2