NHS England

Evidence review: Abatacept for severe, treatment resistant morphoea (localised scleroderma) (adults and children over 2 years)

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Contents

1. Introduction

Indication and epidemiology

Morphoea (or localised scleroderma) is an autoimmune disorder of the connective tissues that causes an initial inflammatory reaction and then sclerotic changes (Torok et al., 2019, Florez-Pollack et al., 2018, Knobler et al., 2017). It is most commonly limited to the skin and subcutaneous fatty tissue, but can also affect the surrounding muscle, fascia, tendons and bone (Knobler et al., 2017, Zulian et al., 2005). Involvement of the internal organs (heart, lung, kidneys) is not a feature (Kreuter et al., 2016, Orteu, 2016). The cause and triggers are not well understood, but there may be a genetic pre-disposition (Weibel and Harper, 2008, Orteu, 2016). Onset has also been associated with certain drugs (bleomycin, carbidopa, penicillamine), chemicals (polyvinyl chloride, solvents, pesticides), infections (borrelia), trauma and radiation (Knobler et al., 2017, Orteu, 2016, Fett and Werth, 2011a). It is hypothesised that such stimuli may activate T-cell cells, which in turn trigger pro-inflammatory and pro-fibrotic mechanisms that promote collagen production (and inhibit its breakdown) in susceptible individuals (Torok et al., 2019, Knobler et al., 2017).

The term morphoea covers a wide spectrum of clinical disease. Several classification systems have been used to define the different subtypes of morphoea (Asano et al., 2018). The Padua Consensus Classification system describes five subtypes (Albuquerque et al., 2019);

I. *Circumscribed morphoea*: one to few discrete plaques (usually superficial) occurring on the trunk or limbs.
II. *Generalised morphoea*: four or more plaques occurring at more than two of seven anatomical sites (head & neck, each limb, anterior trunk and posterior trunk). Also known as disseminated morphoea.
III. *Pansclerotic morphoea*: circumferential involvement of a majority of body sites. This is a particularly severe, disabling subtype that is often rapidly progressive and often involves deep tissue (fascia, muscle, bone)
IV. *Linear morphoea*: Linear streaks of fibrosis that can involve the head and neck or trunks and limbs (occasionally both). Lesions can cause severe growth restriction in children, limb length asymmetry, flexion contractures and impaired mobility.

Linear morphoea affecting the head and neck (including *morphoea en coup de sabre*) can cause scarring alopecia, seizures, migraine, ocular and dental problems and facial asymmetry.

V. *Mixed morphoea*: The presence of two or more subtypes.

In some classifications of morphoea, the term 'generalised morphoea' is used to include both disseminated plaque and pansclerotic forms of the disease (Asano et al., 2018). Since these subtypes are very different in terms of their severity and potential impact on function and quality of life, it is more helpful to classify them separately and avoid using the term 'generalised morphoea'. All subtypes described above can have superficial or deep tissue involvement. However, linear and pansclerotic forms are the most likely to involve deep structures such as fascia, muscle and bone (Albuquerque et al., 2019, Knobler et al., 2017, Orteu, 2016).

The impact and severity of morphoea is variable (Albuquerque et al., 2019). This review focuses specifically on severe and progressive forms of morphoea, including disseminated, pansclerotic or linear subtypes. Severe disease can be defined as presentation with widespread or deep disseminated plaque morphoea, pansclerotic morphoea, craniofacial or limb linear morphoea with evidence of high morbidity such as CNS involvement, facial asymmetry, limb shortening, muscle asymmetry or joint contracture. Speed of progression, functional impairment and psychosocial impact are other important determinants (Orteu 2016, Albuquerque 2019).

Epidemiological data relating to the incidence of morphoea is scarce, but studies in non-UK populations have shown annual incidence rates ranging from 0.4 to 2.7 per 100,000 population (Murray and Laxer, 2002, Peterson et al., 1997). The incidence of morphoea in children may be lower, with one study based in the UK and Ireland reporting an annual incidence rate of 0.34 per 100,000 children under the age of 16 (0.25 per 100,000 for linear disease) (Herrick et al., 2010). People can be affected at any age, but limited plaque morphoea is the most common subtype in adults, and linear morphoea is the most common subtype in children (Fett and Werth, 2011a). Most adults present with morphoea in their 40s, while most children will present between the ages of 2 and 14 (Fett and Werth, 2011a). Females are more commonly affected than males (ratio of about 3:1), and

the disease appears to be more common in white people compared to other ethnic groups (Orteu, 2016, Fett and Werth, 2011a).

Existing guidance from the National Institute for Health and Care Excellence (NICE)

No guidelines from NICE were found on the management of morphoea (or on the use of abatacept for this condition).

Standard treatment and pathway of care

The prognosis of morphoea depends on the subtype and varies from patient to patient (Albuquerque et al., 2019). In about half of cases, the disease can become inactive within 3-5 years (Asano et al., 2018, Peterson et al., 1997). However, the condition (particularly the more severe forms) can follow a more protracted course, becoming chronically active over many years or exhibiting a relapsing-remitting course (despite initially successful treatment) (Asano et al., 2018, Orteu, 2016, Mertens et al., 2015). Even when disease activity remits, permanent deformity and functional abnormalities may persist (Albuquerque et al., 2019).

Current standard treatments for milder forms of morphoea include topical and intralesional steroids, topical calcipotriol, imiquimod and tacrolimus (Albuquerque et al., 2019, Knobler et al., 2017). Phototherapy, including UVA1, broad-band UVA and psoralen with UVA (PUVA) can also be used (Albuquerque et al., 2019, Knobler et al., 2017).

For more severe or progressive disease (especially if there is associated deformity or disability), systemic treatment with corticosteroids, methotrexate or mycophenolate mofetil (either alone or in combination) are often considered (Knobler et al., 2017, Kreuter et al., 2016). Other options include systemic agents such as hydroxychloroquine and ciclosporin (Knobler et al., 2017).

Physiotherapy, connective tissue massage and manual lymphatic drainage are also sometimes used in addition to topical or systemic treatments in severe disease (Florez-Pollack et al., 2018, Knobler et al., 2017). Orthopaedic or plastic surgery may be required

in cases of linear morphoea (once the disease is inactive) to correct deformity and improve cosmetic appearance (Florez-Pollack et al., 2018, Knobler et al., 2017).

The intervention (and licensed indication)

Abatacept belongs to the biological medicines group. It is a fusion protein that acts as a T cell co-stimulation blocker to inhibit TNF-alpha and prevent T cell activation. It can be given via intravenous or subcutaneous injection (Joint-Formulary-Committee, 2019). Prescribing instructions in the British National Formulary (BNF) suggest that subcutaneous injections are given weekly (125mg weekly for adults and according to weight for children) (Joint-Formulary-Committee, 2019, Paediatric-Formulary-Committee, 2019). Alternatively, intravenous injections can be given every two weeks (dose dependent on weight) for three doses, and then monthly thereafter (Joint-Formulary-Committee, 2019). This may be a good option for patients in whom subcutaneous administration is contraindicated or not tolerated. In severe cases, an initial intravenous regime of abatacept may be administered at baseline, week 2 and week 4 followed by weekly subcutaneous injections.

Abatacept is currently licenced (and approved by NICE) for the treatment of rheumatoid and psoriatic arthritis in adults and juvenile idiopathic arthritis in children if certain criteria are met (Joint-Formulary-Committee, 2019, Paediatric-Formulary-Committee, 2019, NICE, 2016, NICE, 2015, NICE, 2010). According to the BNF, side effects can include; asthenia, cough, diarrhoea, dizziness, gastrointestinal discomfort, headaches, hypertension, increased risk of infection, nausea, oral ulceration, skin reactions and vomiting. It is contraindicated in severe intercurrent infection (Joint-Formulary-Committee, 2019).

It is not currently licenced for use in morphoea but is a recognised treatment option in a subset of patients with severe treatment resistant disease (Knobler et al., 2017).

The aim of this review is to examine the current evidence relating to the clinical effectiveness, safety and cost effectiveness of abatacept for the treatment of adults and children (over the age of 2) with progressive, severe disabling forms of morphoea (generalised, pansclerotic or linear subtypes), where there is active disease despite the current standard treatment. For the purpose of this review, ‘severe’ refers to disease

which: (i) causes significant asymmetry of limbs, head and neck or (ii) crosses joints and limits mobility or (iii) involves 3 sites, is circumferential or involves deep structures.

2. Summary of results

Three studies were included in this review (Fage et al., 2018, Adeeb et al., 2017, Stausbol-Gron et al., 2011). All were case series conducted at single centres. No systematic reviews, randomised controlled trials, controlled clinical trials, case-control or cohort studies were found. The included studies involved a total of eighteen patients with severe morphoea, sixteen of whom met the population criteria specified in the PICO document. All three studies reported the outcomes and side-effects in patients started on intravenous abatacept (no comparator groups were included).

Clinical effectiveness

Fage et al. (2018), reported the modified Rodnan Skin Score (mRSS) in four patients with severe morphoea. Three patients had clinically important improvements in their scores after starting abatacept, and one had no change. A complete set of Localised Scleroderma Cutaneous Assessment Tool (LoSCAT) scores were recorded in seven patients at baseline and then again after starting abatacept treatment. There were clinically relevant improvements in disease activity scores in five of these patients, and clinically relevant improvements in damage scores in one patient. Two patients with morphoea en coup de sabre had lesion size measured at baseline and again after starting abatacept treatment. One patient had a reduction in the size of two lesions (47% and 61% respectively) after 3-months follow-up, and the other patient had a reduction in lesion size of 42% after 21-months follow-up. The authors in this study found that five patients reported a ‘good effect’ from treatment. One patient described softening of skin and another described a reduction in skin, muscle and joint symptoms as well as improvements in general wellbeing. A patient with morphoea en coupe de sabre described regrowth of hair.

Adeeb et al., (2017) reported only descriptive outcomes for the one patient in their study that met the PICO population criteria for this review. They found that the plaques in a

patient with mixed disease (linear and circumscribed morphea with deep tissue involvement) stopped progressing within 3-months of starting abatacept treatment and then regressed. They also found that at 6-months the patient reported significant improvements in pain, pruritus and skin texture and she was able to halve the dose of her oral steroids.

Two further patients with severe morphoea were included in this case series (Adeeb et al., 2017). However, due to the severity of their disease and known lack of effective treatment options, both patients were started on abatacept first line meaning that they were not 'treatment resistant'. As such, they do not strictly meet the PICO population criteria for this review. The associated evidence should therefore be viewed as indirectly applicable to the population of interest. The first of these patients had an initial 37% reduction in the mean mRSS score after 6 months, and then a further 58% reduction in the score at 18 months. They also had visible improvements on whole body MRI after 6-months of treatment, and substantial and progressive improvements in Visual Analogue Scale (VAS) scores (measuring disease activity and pain) after 6 and 18 months. She was reported to have significant improvements in her mobility and was able to reduce her dose of prednisolone. The second patient was reported to have improvements in skin texture, inflammation and lymphoedema 'within a few months' of starting abatacept and low dose (5mg/day) prednisolone. The responses in these patients were described as rapid, dramatic and with increased depth of improvement over time.

Stausbol-Gron et al. (2011) measured mRSS in two patients with chronic, progressive disseminated morphoea profunda at baseline and again after starting treatment with abatacept. Both had clinically important reductions in their scores after 19 months (89%) and 7 months (54%) follow-up respectively. The first patient reported improvements in itch, joint mobility and had softening of old lesions. The second patient had improvements in her mobility and was able to walk longer distances. Both patients were able to gradually reduce and stop their systemic steroids.

Adverse events and side effects

Fage et al. (2018) found that nine of the thirteen participants in their study experienced side-effects. Most were minor (sore throat, fatigue, myalgia, diarrhea, nausea, headache, hypertension, oral ulcers, herpes labialis), and only one patient stopped their treatment

because of side-effects. A further patient stopped abatacept due to the development of ulcerative colitis. However, this patient had gastro-intestinal symptoms prior to starting treatment and a family history of the disease.

Adeeb et al (2017) reported that there were no adverse events during abatacept treatment in the three patients included in their study.

Stausbol-Gron et al (2011) stated that the treatment was well tolerated in both their patients. However, one of these patients was diagnosed with breast cancer after 2.5 months, meaning that treatment had to be stopped. The authors felt that the development of breast cancer was not related to treatment. The second patient developed hypertension (a known side-effect of abatacept). This required drug treatment, but the patient was able to continue taking abatacept.

Cost-effectiveness

No studies relating to the cost effectiveness of abatacept in morphoea were found.

Limitations

There are limitations to the evidence presented in the included studies. Sample sizes were very small, and it was unclear in some patients whether there were comorbidities and what concurrent treatments were being used. Neither the patients nor the outcome assessors were blinded to the treatment received, and a comparator group of patients (who did not receive abatacept) was not included in any of the studies. It is therefore possible that any changes observed during abatacept treatment could have been related to the delayed effects of earlier treatments, to the concurrent use of other treatments, or to chance. In addition, no final conclusions can be drawn about the relative effectiveness of abatacept compared to other treatment strategies in this patient population.

3. Methodology

- The methodology to undertake this review is specified by NHS England in their 'Guidance on conducting evidence reviews for Specialised Services Commissioning Products' (2016).
- The searches for evidence were informed by the Population, Intervention, Comparison and Outcomes (PICO) document prepared by NHS England's Policy Working Group for the topic (shown in Section 9).
- Date limits were applied to the search from 1st January 2010 until 31st December 2019. Further details of the search strategy are shown in Section 10.
- Results from the literature searches were screened using their titles and abstracts for relevance against the criteria in the PICO framework. Full text references of potentially relevant studies were obtained and reviewed to determine whether they met the inclusion criteria for the review (further details in Section 10).
- Relevant details and outcomes were extracted from the included studies and recorded in the evidence summary tables (Section 7). The studies were critically appraised, and their quality assessed using National Service Framework for Long Term Conditions (NSF-LTC) evidence assessment framework (Section 7).
- The body of evidence for individual outcomes identified in the papers was graded and recorded in grade of evidence tables (Section 8).

4. Results

Three case series met the inclusion criteria for this rapid evidence review (Fage et al., 2018, Adeeb et al., 2017, Stausbol-Gron et al., 2011). One of these had a prospective design (Adeeb et al., 2017), one was retrospective (Fage et al., 2018) and the other was of unclear design (Stausbol-Gron et al., 2011). In each study, participants were recruited from a single centre (two studies were conducted at the same hospital in Denmark, and one was conducted in Ireland). No systematic reviews, randomised controlled trials, controlled clinical trials, case-control or cohort studies were found.

The three included case series present a total of eighteen patients, sixteen of whom meet the population criteria specified in the PICO. Of the patients that satisfy the PICO criteria, fourteen were women and two were men. The age range was 17-64 (mean age 39). Eight patients had generalised disease (two with lichen sclerosis et atrophicus overlap and two with deep linear overlap), four had linear disease (one affecting the extremities and three with en coupe de sabre), one had mixed linear and plaque disease with deep tissue involvement (affecting the extremities and trunk), one had deep morphoea and two had disseminated morphoea profunda. All patients received intravenous abatacept injections which were dosed according to weight. Some patients switched to subcutaneous injections during treatment. Two patients received prednisolone with abatacept and one received a combination of methotrexate and prednisolone with abatacept. Concurrent treatment regimens were not clear in the remaining thirteen. Maximum follow-up for individual patients ranged from 1 to 32 months (mean 13.4 months). One patient was awaiting follow-up.

Outcomes recorded in these sixteen patients included:

- Clinical effectiveness measured by;
  - Modified Rodnan Skin Score (mRSS),
  - Localised Scleroderma Cutaneous Assessment Tool (LoSCAT),
  - Change in lesion size,
  - Reduction in steroid or disease modifying anti-rheumatic drug (DMARD) use
  - Descriptive improvements.
- Safety measured by reporting of adverse events or side effects.

Two additional patients from one of the included studies (Adeeb et al., 2017) did not meet the specified PICO population criteria. This is because both patients received abatacept as first line treatment for their morphoea (due to its extreme severity at presentation and known lack of effective treatment options), and therefore could not be strictly deemed to have '*active disease despite treatment with current standard of care'*. One of these patients (a 55-year old woman) had extremely severe generalised morphoea with deep tissue involvement. The other (a 48-year old woman) had rapidly progressing deep tissue disease. Both were treated with intravenous abatacept and reducing doses of prednisolone. One was followed up for eighteen months, and the other for six months. Outcomes were measured using mRSS, whole body MRI and Visual Analogue Scale

(VAS) scores for the first patient and were reported descriptively for the second patient. Despite not strictly meeting the PICO criteria, the outcomes in these two patients have been included in this review because both patients meet the severe clinical phenotype specified in the PICO document. This makes the findings highly relevant to patients with severe disease. However, the associated evidence linked to these two cases should be seen as indirectly applicable to the population of interest. Where they have been discussed, this has been made clear.

In patients of all ages with severe morphoea, what is the clinical effectiveness of abatacept compared with current standard treatment with systemic steroids and DMARDs (methotrexate, ciclosporin, mycophenolate, hydroxychloroquine)?

None of the included studies involved a comparator group to compare abatacept with current standard treatment (or placebo). However, all but two patients had tried various treatments prior to abatacept (including topical treatments, phototherapy, methotrexate, hydroxychloroquine, azathioprine, cyclosporine, mycophenolate mofetil, penicillamine and systemic steroids). All three studies reported outcome measures before and after treatment with abatacept was started.

Modified Rodnan Skin Score (mRSS) *(3 studies, total n=7, sample sizes n=1, n=2, n=4).*

The mRSS is a measure of skin thickness often used as an outcome measure in systemic sclerosis (Khanna et al., 2017). Measurements are made by palpation in 17 anatomical areas. Thickness is rated from 0-3 (0=normal; 1=mildly increased skin thickness; 2=moderately increased skin thickness; 3=severely increased skin thickness). The scores from each area are then totalled to give a score out of 51 (Khanna et al., 2017). Clinically meaningful improvements in systemic sclerosis correlate with an mRSS score change of 3-4 points (the usual interval between scores should be more than 3-months) (Khanna et al., 2019, Khanna et al., 2017). The mRSS has commonly been used in clinical practice to evaluate outcomes in morphoea (Hawley et al., 2014), and can provide valuable information on disease activity. However, it was developed and validated for use in systemic sclerosis and has not been validated in morphoea (Fett and Werth, 2011b).

Fage et al (2018) measured mRSS in four patients. Three of these had generalised morphoea (one with lichen sclerosis et atrophicus overlap and one with deep linear

overlap), and one had linear disease. Scores were measured at baseline and at one other time after abatacept was commenced. Two of the patients with generalised disease improved (change in score from 9 to 5 points after 22-month follow-up; and 18 to 2 points after 19-month follow-up), and one had no change after 32-month follow-up. The patient with linear disease had a reduction in mRSS score from 5 to 1.5 points after 13 months.

Stausbol-Gron et al. (2011) measured mRSS in two patients with chronic and progressive disseminated morphoea profunda. Patient one had a reduction in score from 18 to 2 points after 19 months of treatment and patient two had a reduction from 13 to 6 points after 7 months (but only 2.5 months of treatment). Both of these patients also received a tapering dose of prednisolone (15mg and 7.5mg) alongside their abatacept treatment but were able to stop their steroid medication after 11 and 4 doses of abatacept respectively.

Adeeb et al. (2017) measured mRSS in one patient with severe generalised disease with deep tissue involvement. This patient started abatacept first line due to the severity of disease and lack of effective treatment options meaning that they did not meet the PICO population criteria for this review. The associated evidence is therefore indirectly applicable to the population of interest. The mean mRSS (after testing by three different clinicians) was 38 points at baseline. This reduced to 24 points at six months and then to 10 points at eighteen months follow-up, suggesting continued and progressive improvements over time. High dose prednisolone (60mg/day) was started at the same time as the abatacept but was tapered slowly down to 10mg/day over the first 3 months.

Localised Scleroderma Cutaneous Assessment Tool (LoSCAT) *(1 study, total n=7).*

The LoSCAT has been developed and validated specifically for use in morphoea and is recommended for assessing severity and disease activity in both the European and German morphoea guidelines (Torok, 2020, Teske and Jacobe, 2019, Knobler et al., 2017, Kreuter et al., 2016). It combines the modified Localised Scleroderma Skin Severity Index (mLoSSI) , which assesses cutaneous activity (erythema, thickness and new lesion/lesion extension), the Localised Scleroderma Skin Damage Index (LoSDI) which assesses damage (dermal atrophy, subcutaneous atrophy and dyspigmentation), and the Physician's Global Assessment (PGA) tool (Foeldvari, 2019, Kelsey and Torok, 2013). Both the mLoSSI and the LoSDI have been shown to have good reliability and validity in morphoea studies (Kelsey and Torok, 2013, Fett and Werth, 2011b). Clinically significant

improvements are indicated by decreases in activity scores of at least 2 points, and decreases in damage scores of at least 2 points (Teske and Jacobe, 2019).

Fage et al (2018) measured a *complete* set of LoSCAT scores in seven patients; once at baseline and a second time after abatacept treatment had started. Five of these patients had generalised disease (one with lichen sclerosis et atrophicus overlap), one had deep morphoea and one had linear disease. In the patients with generalised disease, activity scores improved in four patients (range of improvement 3-12 points, mean improvement = 7 points, mean follow-up 12 months), and worsened in one patient (increase in score from 13 to 20 points after 16 months). Damage scores improved in one patient (reduction in score from 11 to 9 points after 25 months), stayed the same in one (follow-up 3 months) and worsened in three others (mean increase 4.7 points, mean follow-up 12 months). The patient with deep morphoea had an improvement in activity score from 18 to 3 points, and an improvement in damage score from 14 to 13 points after 9 months follow-up. The patient with linear morphoea had no change in activity scores after 18 months (although both scores were zero), and a reduction in damage score from 22 to 21 points. A further two patients had an incomplete set of LoSCAT scores recorded.

Change in the size of lesions *(1 study, total n=2).*

Fage et al. (2018) used the change in lesion size from baseline to follow-up to measure clinical effectiveness in two patients with linear morphoea (en coup de sabre). One patient had a reduction in one lesion from 50.4 cm^2 to 26.6 cm^2 (47% decrease) and in another lesion from 52.5 cm^2 to 20.5 cm^2 (61% decrease) after 3-months follow-up. The other patient had a reduction in lesion size from 41.4 cm^2 to 24 cm^2 (42% decrease) after 21-months follow-up.

Reduction in steroid or DMARD use *(2 studies, total n=5, sample sizes n=3, n=2).*

Adeeb et al. (2017) (n=3) reported the case of one patient with mixed subtype morphoea (circumscribed and linear disease with deep tissue involvement) who was commenced on abatacept alongside her current treatment of methotrexate 15mg weekly and prednisolone 10mg daily. Over the course of six months, the patient was able to reduce her dose of prednisolone to 5mg daily and maintain the same dose of methotrexate. The outcomes of two further patients treated with abatacept and prednisolone for severe

morphoea were reported in this study. However, these patients were started on abatacept first line (due to the severity of their disease), meaning that they did not meet the PICO population criteria. The associated evidence is therefore indirectly applicable to the population of interest. The first patient had deep morphoea and was started on low dose (5mg/day) prednisolone with abatacept, but no information was provided about ongoing steroid use at follow-up. The second patient (with severe generalised morphoea), was started on 60mg prednisolone with abatacept. Over a period of three months, this was gradually tapered to a 10mg daily maintenance dose.

Stausbol-Gron et al. (2011) (n=2) commenced prednisolone alongside abatacept in two patients with disseminated morphoea profunda. The first patient was started on 15mg prednisolone and was able to taper this down to zero before the 11th abatacept treatment. The second patient was started on 7.5mg prednisolone and was able to stop this after four doses of abatacept.

Descriptive improvements in symptoms, function and quality of life *(3 studies, total n=18, sample sizes n=13, n=2, n=3).*

All three studies gave a descriptive commentary on clinical effectiveness outcomes. Fage et al. (2018) (n=13) state that five patients reported a 'good effect' from abatacept treatment (four with generalised morphoea and one with deep disease). One patient described softening of skin and another described a reduction in skin, muscle and joint symptoms as well as improvements in general wellbeing. A patient with morphoea en coupe de sabre described regrowth of hair.

Adeeb et al. (2017) (n=3) reported that an enlarging, widespread plaque in a patient with mixed localised and linear disease stopped progressing within 3-months of starting abatacept and then started regressing. At 6-months the patient also reported significant improvements in pain, pruritis and skin texture. Descriptive outcomes were reported in a further two patients with severe presentations. However, these patients were started on abatacept first line (due to the severity of disease), meaning that they did not meet the PICO population criteria. The associated evidence is therefore indirectly applicable to the population of interest. The first of these had deep morphoea, and was found to have improvements in skin texture, inflammation and lymphoedema 'within a few months' of starting abatacept and low dose (5mg/day) prednisolone. The second of these patients

(with severe generalised morphoea), was reported to have dramatic clinical improvements within 6-months of starting abatacept, leading to significant improvements in mobility (due to resolution of contractures), skin softening and hair re-growth.

Finally, Stausbol-Gron et al. (2011) (n=2), reported that one patient with disseminated morphoea profunda experienced a reduction in itch and an improvement in joint mobility after starting abatacept (alongside prednisolone). They also found that erythema and disease activity were reduced, and that old lesions were softened. Their second patient (also with morphoea profunda) had disappearance of inflammatory lesions, improved mobility of the shoulders, hips and knees and increased walking distances. Both patients were able to gradually reduce and stop their systemic steroids.

Other measures of disease activity (1 study, total n=1)

MRI scanning can provide an objective measure of depth and breadth of involvement as well as inflammation, sclerosis and atrophy in morphoea (Asano et al., 2018, Florez-Pollack et al., 2018, Shahidi-Dadras et al., 2018). Changes seen on MRI can therefore be a useful outcome measure for monitoring the response to therapy, especially when clinical examination is limited due to the depth of disease (Asano et al., 2018, Florez-Pollack et al., 2018, Shahidi-Dadras et al., 2018).

Adeeb et al. (2017) performed baseline whole-body MRI and VAS scores in one patient with severe generalised morphoea with deep tissue involvement. This patient was started on abatacept first line due to the extremely severe presentation, and lack of effective treatment options. This means that they did not meet the PICO population criteria for this review, and the associated evidence is only indirectly applicable to the population of interest. The patient was started on abatacept alongside a tapering dose of prednisolone, pregabalin for pain and fexofenadine for itch. At 6-months follow-up, the full body MRI showed significant improvements in disease activity compared to baseline, including reduced skin thickening, fasciitis and oedema.

VAS scores, which included Patient Global Disease Activity (PGDA), Patient Global Pain (PGP), Patient Day Pain (PDP), Patient Night Pain (PNP) and Physician Global Disease Activity (PhGDA) were recorded at baseline and then again at 6 and 18-months. Improvements in all scores were noted after 6 months of treatment (50%, 60%, 82%, 66%

and 80% respectively). This improvement continued over the next year, and by 18 months all scores had reduced by either 88% (PGP and PDP) or 100% (PGDA, PNP and PhGDA) compared to baseline.

In patients of all ages with severe morphoea, what is the safety of abatacept compared with current standard treatment with systemic steroids and DMARDs (methotrexate, ciclosporin, mycophenolate, hydroxychloroquine)?

Adverse events *(3 studies, total n=18, sample sizes n=13, n=2, n=3).*

Fage et al (2018) (n=13) reported that one patient was diagnosed with ulcerative colitis during abatacept treatment, meaning that the drug had to be stopped. The authors state that this patient had gastro-intestinal symptoms prior to starting abatacept, and that there was a family history of disease.

Adeeb et al (2017) (n=3) reported that there were no adverse events, but do not give further details.

Stausbol-Gron et al (2011) (n=2) reported that one patient was diagnosed with breast cancer 2.5 months after starting abatacept, meaning that treatment had to be stopped. However, the authors felt that the cancer was unrelated to treatment.

Side-effects *(3 studies, total n=18, sample sizes n=13, n=2, n=3).*

Of the 13 patients included in the study conducted by Fage et al (2018), nine people reported possible side-effects:

- Oral ulcers (n=1)
- Sore throat (n=1)
- Fatigue (n=3)
- Myalgia (n=2)
- Diarrhoea (n=1)
- Hypertension (n=1)
- Headache (n=1)
- Herpes labialis (n=1)
- Sensations of progressive tightening of the skin and tingling (1)
- Nausea/vomiting (n=1)

One patient in this study stopped treatment due to side-effects.

In the other two studies, the authors report that treatment with abatacept was well tolerated (n=5), but do not give further details (Adeeb et al., 2017, Stausbol-Gron et al., 2011). One patient in these studies developed hypertension (a known side effect of abatacept) and required drug therapy (Stausbol-Gron et al., 2011). However, she was able to continue her abatacept as her blood pressure stabilised on treatment.

In patients of all ages with severe morphoea, what is the cost effectiveness of abatacept compared current standard treatment with systemic steroids and DMARDs (methotrexate, ciclosporin, mycophenolate, hydroxychloroquine)?

No studies were identified that investigated the cost effectiveness of abatacept.

From the evidence selected is there evidence to suggest there are particular subgroups of patients that would benefit from treatment with abatacept? (For example, by morphoea subtype – generalised, pansclerotic and linear)

No studies were identified that formally compared outcomes between subgroups.

The included studies report the characteristics of participants in terms of their gender, age and subtype of morphoea. However, small sample sizes make it difficult to comment on whether particular subgroups appear to benefit more than others. Improvements with abatacept are variously reported in all subtypes of severe morphoea, in men and women and across a range of ages.

No studies involving paediatric patients were found in this evidence review (although one of the adult cases first presented at the age of eight years). It has been suggested that the results from adult morphoea trials could be extrapolated to paediatric populations because the pathophysiology of the disease is assumed to be the same (Foeldvari, 2019).

5. Discussion

This review has included three case series which investigate the use of abatacept in adults with progressive, severe disabling forms of morphoea, where there is active disease despite the current standard treatment (Fage et al., 2018, Adeeb et al., 2017,

Stausbol-Gron et al., 2011). These studies present a total of 18 patients, including two patients who meet the criteria for the severe clinical phenotype specified in the PICO document, but who were not treated with standard therapies prior to initiation of abatacept. Whilst the current classification criteria for morphoea continues to be refined, the patients described in these case series all had either disseminated, deep or rapidly progressive disease (or all three) and therefore qualify as the severe subpopulations specified in the PICO document.

The findings from the included studies suggest that treatment with abatacept can be associated with rapid and significant clinical improvements in patients with severe morphoea. These include both a reduction in disease activity and functional improvements (which in some patients can be dramatic and sustained). Of the seven patients who had mRSS scores recorded, six had clinically relevant improvements in their scores after a mean follow-up of 18.6 months. Of the seven patients who had a complete set of LoSCAT scores recorded, five had clinically relevant improvements in their activity scores, and one had clinically relevant improvements in their damage scores after a mean follow-up of 12.9 months. Notably, these improvements were often far in excess of the minimum clinically important differences for mRSS and LoSCAT scores.

Other outcomes measures in the included studies also indicate improvements in clinical condition after treatment with abatacept. Two patients with linear morphoea (en coup de sabre) had a mean reduction in lesion size of 50% after mean follow-up of 12 months. In addition, one patient with extremely severe generalised/deep disease was reported to have improvements on whole body MRI and in pain and disease activity (measured using VAS scores). Descriptive outcomes were also largely positive. Due to the small sample sizes, it was not possible to identify whether response to treatment varied according to subgroup (such as morphoea subtype or age).

Ten of the eighteen patients included in this review reported possible side-effects whilst taking abatacept. These included sore throat, fatigue, myalgia, diarrhoea, nausea, headache, hypertension, oral ulcers and herpes labialis. However, these seemed to be relatively mild and only one patient stopped treatment due to side-effects). No serious adverse events were directly attributable to abatacept. This is consistent with observations from one recent randomised, double-blind, placebo-controlled trial of abatacept in early diffuse cutaneous systemic sclerosis that reported a comparable

adverse effect profile to placebo (Khanna et al., 2020). Evidence also suggests that abatacept is associated with fewer adverse events (infection and infusion/injection site reactions) compared to other biologic medications in patients with rheumatoid arthritis (Chen et al., 2020, Ozen et al., 2019).

When considering the overall beneficial results of the included studies, it is also important to keep in mind their limitations. Sample sizes were very small, increasing the risk that the positive treatment effects could have been due to chance, and reducing the reliability of the findings. Furthermore, both the patients and the outcome assessors were aware of the treatments that were being used. This could have influenced their recording of outcome measures and biased the results (most likely in favour of a positive treatment effect). The mRSS has not been validated for use in morphoea, and therefore may not provide an accurate reflection of disease activity. This is echoed in the finding that one patient had no change in mRSS scores after 32 months of treatment, yet they still reported a good response to treatment (Fage et al., 2018). A comparator group of patients (who did not receive abatacept) was not included in any of the studies. Without a comparator group, it is possible that any changes observed during abatacept treatment could have been due to the natural history of the disease (although follow-up was generally short relative to the duration of disease activity), to the delayed effects of earlier treatments, to the concurrent use of other treatments, or to chance. For example, five of the patients included in this review received prednisolone alongside their abatacept. Since prednisolone is a recognised treatment for morphoea, this may have impacted the outcomes. For the remaining thirteen patients, no details are given about whether they received other medication with their abatacept.

The current evidence is considered to be clinically relevant to all patients with severe treatment resistant morphoea. However, sample sizes were small, and all the included studies were conducted in adult patients. Although the disease process is thought to be the same in adults and children, the findings cannot be directly extrapolated to paediatric populations with any certainty. Finally, although all three studies were conducted in European centres, none were UK-based, meaning that the findings may not be generalisable to English patients receiving NHS care.

The rationale for the development of the existing evidence base has been a lack of effective treatments for people with severe morphoea, especially if they do not respond

adequately to (or are intolerant of) standard treatment. The findings of the studies included in this review have gone beyond proof of concept and serve to highlight compelling evidence of clinically significant benefits and safety for abatacept in patients with severe resistant disease. They are also consistent with the hypothesis that T-cells are key regulators in the autoimmune pathogenesis of morphoea and hence provide biological plausibility.

Nevertheless, a substantial amount of confirmatory, high quality research is still very much required on this topic to confirm these results and establish where abatacept should be positioned on the severe morphoea treatment pathway. Larger, good quality, randomised, controlled trials are needed to clarify/quantify treatment effects and to compare long and short-term outcomes with those receiving standard care. Future studies should also investigate the cost effectiveness of using abatacept in this patient population and the effectiveness of abatacept in children (and other sub-populations) with severe morphoea. They should additionally aim to explore the acceptability of treatment as well as to confirm that the rate and type of side-effects or adverse events are similar to abatacept use in licenced indications. It is important that further research and developmental strategies are discussed with NHS England decision makers and commercial partners to establish how this may be best carried out in NHS settings.

6. Conclusion

Morphoea is a rare autoimmune disorder of the connective tissues that can affect people at any age. It causes a wide spectrum of disease, but at its most severe can cause significant morbidity, disability, long-term deformity and psychological effects. There is therefore a high unmet need to identify new and novel treatment options for those with severe, treatment resistant progressive disease, in whom standard treatment has failed or has not been tolerated.

This review has identified and critically appraised the available evidence relating to the clinical effectiveness, safety and cost effectiveness of abatacept for the treatment of people with progressive, severe disabling forms of morphoea, where there is active disease despite the current standard treatments.

The evidence included in this review suggests that abatacept may be an effective treatment for patients with severe, progressive and treatment resistant/ refractory morphoea. It also provides some indication of the clinical outcomes that could be expected to be achieved following its use in both acute (inflammatory) and chronic (sclerotic) phases. Potential clinical benefits include improvements in; (i) symptoms (pain, pruritus and wellbeing), (ii) signs (lesion size, skin texture, inflammation, hair re-growth and reduced plaque progression/ regression) (iii) function (joint movements and walking distances) and (iv) reduction/cessation of systemic steroids. It is notable that these outcomes in response to abatacept go beyond proof of concept and support biological plausibility that molecular T-cell regulatory pathways are involved in the pathogenesis of morphoea.

The available evidence also indicates that some patients treated with abatacept experience mild side-effects. However, these did not appear to preclude the continuation of treatment. There is insufficient evidence to determine whether particular subgroups of patients with severe morphoea benefit differentially from treatment. No studies were identified that investigated the cost effectiveness of abatacept.

It is important to emphasise that although promising, this is preliminary evidence and hence could have been affected by methodological weaknesses in the included studies. These studies being case series also provide no comparative information on the effectiveness of abatacept compared to alternative treatment strategies. Information on its cost-effectiveness in this patient population is also lacking. Further confirmatory, larger and controlled studies are required, although this may be difficult given the rarity of severe morphoea. Controlled access to abatacept in this patient subgroup would provide an opportunity to collect further information on its effectiveness and to refine targeted patient selection. Further high quality evidence is urgently needed given that abatacept has demonstrated a substantial positive effect on outcomes and considering the unmet need of individuals with severe treatment resistant morphoea to access effective treatments.

7. Evidence Summary Table

Use of abatacept for the treatment of adults and children (over the age of 2) with progressive, severe disabling forms of morphoea, where there is active disease despite the current standard treatment (no comparator).									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence**	**Applicability**	**Critical Appraisal Summary**
Fage et al. 2018	P1 Retrospective case series conducted in one centre	n=13 Denmark All patients with treatment resistant localised scleroderma treated with abatacept at the hospital between 2009 and 2016. 11 women and 2 men with treatment resistant,	Patients treated with either 500mg or 750 mg IV abatacept according to weight. Injections given on days 1, 15, 30 and thereafter every 4-6 weeks. Some patients switched to 125mg/week SC injections	Primary Clinical effectiveness	Modified Rodnan Skin Score (mRSS) from medical records[1]	3/8 patients with generalised disease had mRSS measured. Two improved and one stayed the same (mean reduction 6.7 over a mean duration of 24 months). 1/5 patients with linear or deep disease had mRSS measured. Reduction in score from 5 to 1.5 after 13 months.	5/10 medium	Direct	The sample size was very small, consisting of only thirteen patients. Nonetheless, a mix of patients (with generalised, linear or deep subtypes) were included, and the results were presented according to individual patients and according to subtype. This makes the findings relevant to people with different types of severe morphoea. All patients with treatment resistant morphoea who were started on abatacept between 2009 and 2016 were included (consecutively recruited). This reduced the risk of selection bias; however, inclusion and exclusion criteria were not explicitly stated. It was not clear whether patients included in the study were at the same point in their disease and no details were given about how long ago each participant had been diagnosed. Details of the treatments previously tried by each patient
				Primary Clinical effectiveness	Localised Scleroderma Cutaneous Assessment	6/8 patients with generalised disease had LoSCAT measured. Activity scores decreased in 4 patients and increased in 1 (mean reduction 4.2 over a mean duration of 12.6 months).			

[1] The mRSS is a measure of skin thickness developed for use in patients with systemic sclerosis. Measured by palpation, 17 anatomical areas are rated from 0-3 (0=normal; 1=mildly increased skin thickness; 2=moderately increased skin thickness; 3=severely increased skin thickness). Scored out of 51 (Khanna et al 2017).

		severe, localised scleroderma. Age range 17-64. Mean age 39. 8 patients had generalised disease and 5 had linear or deep subtypes. All appeared to meet the PICO criteria. No details about co-morbidities or ethnicity	during treatment.		Tool (LoSCAT)[2]	Scores were incompletely recorded in one patient. Damage scores increased in 3 patients, reduced in 1 patient and remained the same in 1 patient (mean increase of 2.4). Scores were incompletely recorded in one patient. 3/5 patients with linear or deep disease had LoSCAT measured (one patient measured twice). One patient had a reduction in both activity (18 to 3) and damage scores (14 to 13). One patient had activity scores of zero at both assessments[3], and a reduction in damage score from 22 to 10 at 13 months, and then an increase to 21 at 18 months. The last patient had incompletely recorded activity and damage scores.			were provided – these varied significantly between patients. Neither the patient nor the clinicians/outcome assessors were blinded to the treatment received. This could introduce the possibility of response bias and observer bias favouring a positive treatment effect. Clinical effectiveness outcomes were assessed using mRSS (4 patients) and/or LoSCAT scores (10 patients). This is a more objective, tangible and reliable way of presenting outcomes compared to descriptive reporting. LoSCAT is a validated and reliable scoring system for morphoea. However, mRSS was developed for use in systemic sclerosis and has not been validated in morphoea. The scores were reportedly recorded by 'well trained doctors', improving their reliability. However, there is no mention of how the authors minimised the risk of inter-rater variability. Three of the ten patients with LoSCAT scores had missing data, meaning that improvements could not be assessed in these people. Two patients had no mRSS or LoSCAT scores recorded. Instead, change in size of the lesions was used to assess clinical effectiveness. This could be open to interrater variability and only assesses the response to treatment at 1-2 body locations. Clinical effectiveness assessments were carried out at two points in time for most patients (11/13 had two assessments using one of the clinical effectiveness outcome measures). These were done before starting treatment with abatacept and anywhere between 3 and
				Primary Clinical effectiveness	Change in the size of lesions	The two patients with en coup de sabre had affected areas measured (no MRSS or LoSCAT score). An approximate reduction of 50% of the area affected (in cm^2) was observed in both patients.			

[2] LoSCAT combines the modified Localised Scleroderma Skin Severity Index (mLoSSI) (cutaneous activity), the Localised Scleroderma Skin Damage Index (LoSDI) (damage) and the Physician's Global Assessment (PGA) tool (Foeldvari, 2019). Mild, moderate and severe activity corresponded with LoSCAT activity index (LoSAI) scores of 0-4, 5-12 and 13 and over. Mild, moderate and severe damage corresponded with LoSCAT damage index (LoSDI) scores of 0-10, 11-15 and 16 and over (Teske and Jacobe 2019).

[3] Clinically relevant improved activity is indicated by LoSAI decrease of at least 2 points or 27·5%. Clinically relevant improved damage is indicated by LoSDI score decrease of at least 2 points. Clinically relevant worsening activity is indicated by LoSAI increase of at least 2 points or 19·5. Clinically relevant worsening damage is indicated by LoSDI increase of at least 25·5% (Teske and Jacobe 2019).

				Secondary Clinical effectiveness	Descriptive outcomes	Five patients reported a 'good effect' of treatment, with one patient describing improvements in wellbeing, myalgia and joint pain.			32 months afterwards (mean time between scores 15 months). It is therefore difficult to tell at which time-point any improvements started and whether scores fluctuated over time. A comparator group of patients who did not receive abatacept was not included. Without a comparator group, it is possible that any changes observed during abatacept treatment could be related to the natural history of the disease (although the length of follow-up was short relative to the duration of disease prior to abatacept treatment), to the delayed effects of earlier treatments or to the concurrent use of other treatments. It was not clear whether any of the patients continued on other therapies alongside their abatacept. The authors do not include any analytical statistics to test hypotheses about effectiveness. No detailed information on how side-effect data was collected Not clear if formally assessed or ad-hoc collection of this data. Five patients had stopped treatment and 8 were still receiving treatment at the study end-point. Reason not given in two patients (one stopped due to side effects, one due to diagnosis GI and one due to wish to conceive). Sources of funding were not disclosed. One of the authors performs studies in cooperation with Actelion Roche and Boehringer-Ingelheim, but there were no associations with these companies in this study.
				Secondary Not clear if clinical effectiveness or safety	Changes in CRP, C3c, C4, and/or PIIINP	Authors report that "when measured, these were within reference range and without significant deviation in all patients". No further details given			
				Secondary Safety	Side-effects reported	Possible side-effects reported by 9 people; • Oral ulcers (1) • Sore throat (1) • Fatigue (3) • Myalgia (1) • Diarrhoea (1) • Hypertension (1) • Headache (1) • Herpes labialis (1) • Nausea/vomiting (1) One patient stopped treatment due to the sensations of progressive tightening of the skin, tingling and aching in the legs and fatigue. One patient stopped treatment due to a diagnosis of ulcerative colitis (GI symptoms prior to treatment and a FH of the disease).			

Adeeb et al. 2017	P1 Prospective case series conducted in one centre	n=3, but only one patient (case 3) met the PICO criteria. The other two (cases 1 & 2) were given abatacept first line and therefore did not meet PICO criteria. Ireland. The eligible case (case3) was a 29-year-old Caucasian woman with linear and plaque morphoea with deep tissue involvement. This was progressive despite methotrexate and prednisolone. No information about co-morbidities. Case 1 was a 55-year old Caucasian woman with a 1-year history of disease. No previous	All were started on Abatacept 10mg/kg, and all were given concurrent prednisolone (varying doses). Case 3 also continued her current treatment of methotrexate. Case 1 was given pregabalin for pain and fexofenadine for itch. Assessment was made at baseline and again at 6 months for all patients. Assessment was made again at 18 months for case1.	Primary Clinical effectiveness	Descriptive outcomes	Case 1 (doesn't meet PICO criteria and therefore provides indirect evidence only): Dramatic improvement after 6 months treatment. Skin softening, hair re-growth. Could walk independently without aids following resolution of knee contractures. Prednisolone dose tapered from 60mg/d to 10mg/day over 3 months. Case 2 (doesn't meet PICO criteria and therefore provides indirect evidence only): Within months improvement in induration and texture of the skin with resolution of inflammatory areas and lymphoedema. Case 3: The previously progressive plaques stopped progressing within three months and then began to regress. At 6 months, the patient reportedly noticed dramatic improvements in her pain, pruritis and skin texture. Able to reduce prednisolone from 10mg/d to 5mg/d. Continued methotrexate.at the same dose Note improvements reported in both acute and chronic phases of the disease.	4/10 medium	Cases 1 and 2: indirect Case 3: direct	No details were given about the methods for patient selection (or inclusion/exclusion criteria), and no specified time interval for patient recruitment is stated. This raises the possibility of selection bias. The sample size was very small, consisting of only three patients (of which only one met the PICO criteria). Skin biopsy used in all patients to confirm the diagnosis of morphoea – improved diagnostic accuracy. Neither the patient nor the clinicians/outcome assessors were blinded to the treatment received. This could introduce the possibility of response bias and observer bias favouring a positive treatment effect. In particular, descriptive outcomes may not be a reliable way of measuring outcomes. The authors state that at baseline and 6-months, mRSS was performed independently by three clinicians This improves the reliability of the outcome measures. However, these outcomes were not presented for the PICO eligible patient. In addition, mRSS was developed for use in systemic sclerosis and has not been validated in morphoea. The authors do not include any analytical statistics to test hypotheses about effectiveness. A statement was made to say that there were no adverse events and that the treatment was well tolerated, but no further details were given about any side-effects experienced by the patient. It is not clear whether these were formally assessed. A comparator group of patients who did not receive abatacept was not included. Without a comparator group, it is possible that any changes observed during abatacept treatment could be related to the natural history of the disease, to the delayed effects of earlier treatments or to the concurrent use of steroids. Case 1 and 2 had not tried any previous treatments prior to abatacept. It appears that Case 3 had only recently been diagnosed and that the only treatment received
				Primary Clinical effectiveness	mRSS	Case 1 (doesn't meet PICO criteria and therefore provides indirect evidence only): Baseline mRSS was 38. This reduced to 24 at 6 months and 10 at 18months follow-up.			

		treatments. Diagnosed with generalised morphoea with deep tissue involvement (extremely severe). Case 2 was a 48-year old Caucasian woman with rapidly progressing morphoea with deep tissue involvement.		Primary Clinical effectiveness	MRI	Case 1 (doesn't meet PICO criteria and therefore provides indirect evidence only): At 6-months follow-up, whole body MRI showed improvements in disease activity (including reduced skin thickening, fasciitis and oedema).			prior to abatacept was 3 months of methotrexate with prednisolone. She may therefore have less 'treatment resistant disease' compared to other patients included in this review (who had all tried multiple treatments prior to abatacept). Follow-up was for only 6 months in Case 2 and 3, and 18 months in Case 1. No conclusions about effectiveness beyond these timescales can be drawn. Case 1 demonstrated ongoing improvements with treatment over time. Sources of funding were not disclosed. No statement was made about conflict of interests.
				Primary Clinical effectiveness	Visual Analogue Scale (VAS) scores	Case 1 (doesn't meet PICO criteria and therefore provides indirect evidence only): VAS scores, which included Patient Global Disease Activity (PGDA), Patient Global Pain (PGP), Patient Day Pain (PDP), Patient Night Pain (PNP) and Physician Global Disease Activity (PhGDA) were recorded at baseline and then again at 6 and 18-months. Improvements in all scores were noted after 6 months of treatment, and by 18 months all scores had further reduced. At 18 months all scores had reduced by 88% or 100% compared to baseline.			
				Secondary Safety	Side effects or adverse events	The authors report no adverse events and say the treatment was well tolerated.			
Staus bol-Gron, B et al. 2011.	P1 Case series conducted in one centre (no details	n=2 Denmark Both cases had a diagnosis of disseminated morphoea	Patient (a) received abatacept 750mg IV on days 1, 15 and 30 and thereafter	Primary Clinical effectiveness	Descriptive outcomes	Patient (a) was reportedly less itchy with increased joint motion. Disease activity and erythema decreased, and older lesions became softer. Patient (b) reported better movement of the shoulders, hips	2/10 (poor)	Direct	The research question and aims for this study were not clearly stated. Very few details were given about the methods used. No details were given about patient selection (or inclusion/exclusion criteria) beyond chronic progressive morphoea profunda uncontrolled by previous treatments. No specified time interval for patient recruitment is

	provided about method)	profunda and matched the PICO criteria. Both female. One case 47 (diagnosed at 22 years) and one case 38 years old (diagnosed at 8 years old). No details on ethnicity. Case 1: otherwise well. No details about comorbidities in case 2.	every 4-6 weeks. 20 treatments received. Concurrent taping prednisolone (from 15 mg) up until the 11th treatment. Patient (b) received abatacept 500mg IV on days 1, 15 and 30 and thereafter every 4 weeks. 5 treatments received. Concurrent prednisolone tapering dose (from 7.5 mg) given for the first 4 treatments. Treatment stopped after 2.5 months due to breast cancer diagnosis.			and knees and could walk longer distances. In both patients, concomitant steroids were able to be stopped.			stated. This raises the possibility of selection bias. The sample size was very small, consisting of only two patients with disseminated morphoea profunda. Neither the patient nor the clinicians/outcome assessors were blinded to the treatment received, meaning that there may have been some reporting bias favouring a positive treatment effect. The mRSS scores were assessed by two of the authors separately or together for patient (a), improving the reliability of the results. However, no details were given about how mRSS scores were assessed for patient (b). The mRSS was developed for use in systemic sclerosis and has not been validated in morphoea. No comparator group of patients that did not receive abatacept were included. Without a comparator group, it is possible that any changes observed during/after abatacept treatment could be related to the natural history of the disease (although the length of follow-up was short relative to the duration of disease prior to abatacept treatment), to the delayed effects of earlier treatments or to the concurrent use of steroids. The MRSS for patient (b) was reported at 7 months after treatment started. However, the patient only received 2.5 months of treatment (5 doses of abatacept). It is therefore impossible to know at which point improvements were made and whether these improvements were due to the abatacept. Follow-up was for 19 months in patient (a) and only 2.5 months in patient (b). No conclusions about effectiveness beyond these timescales can be drawn. The authors do not include any analytical statistics to test hypotheses about effectiveness. Sources of funding were not disclosed. No conflicts of interest were declared.
				Primary Clinical effectiveness	mRSS	Patient (a) had an mRSS of 18 before treatment started and 2 after 20 treatments (19 months). Patient (b) had a mRSS of 13 before treatment, which reduced to 6 after 7 months.			
				Primary Safety	Side effects reported	Patient (a) developed hypertension during the treatment period (requiring drug therapy). The treatment was otherwise reported to be well tolerated. Patient (b) had no reported adverse effects during treatment. However, she was diagnosed with breast cancer after 2.5 months of treatment, meaning that treatment with abatacept had to be stopped.			

8. Grade of evidence table

Use of abatacept for the treatment of adults and children (over the age of 2) with progressive, severe disabling forms of morphoea, where there is active disease despite the current standard treatment (no comparator).					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
Changes in mRSS	Fage et al. 2018	5	Direct	C	The modified Rodnan Skin Score (mRSS) is a measure of skin thickness often used as an outcome measure in systemic sclerosis (Khanna et al., 2017)[4]. Clinically meaningful changes in systemic sclerosis correlate with an mRSS score change of 3-4 points (Khanna et al., 2019, Khanna et al., 2017). It is an important outcome measure in morphoea because it can provide an indication of the degree and extent of skin disease. However, the tool was developed and validated for use in systemic sclerosis and has not been validated for evaluating outcomes in morphoea (Fett and Werth, 2011b). Fage et al. (2018), reported the modified Rodnan Skin Score (mRSS) in three patients with generalised morphoea and one patient with linear disease. Scores were measured at baseline and then once again after abatacept was commenced. Three patients (two with generalised disease and one with linear disease) had clinically important improvements in their scores (mean reduction of 7.8 after mean follow-up of 18 months), and one had no change (at 32-month follow-up). There is potential for bias to affect the results of this study. The sample size was small, precluding statistical analysis of the results, increasing the risk that the outcomes could have been due to chance, and reducing the reliability of the findings. There is also no mention of how the authors minimised variability in scoring between clinicians, affecting the reliability of the findings. Also, the results cannot tell us anything about how long it took for improvements to be seen or about whether there were any fluctuations in scores over time. The study also has several limitations common to most case series. First, there is a risk of selection bias because the researchers have selected the patients for treatment. Second, neither the patient nor the outcome assessors were blinded to the treatment received, introducing the possibility of response or observer bias (in favour of a positive treatment effect). Third, a comparator group of patients who did not receive abatacept was not included. It is therefore not possible to know for certain whether the outcomes observed were related to the delayed effects of earlier treatments, to the concurrent use of other treatments, or to chance. In addition, no final conclusions can be drawn about the relative effectiveness of abatacept compared to other treatment strategies.
	Stausbol-Gron et al. 2011	2	Direct		

[4] Measurements are made by palpation in 17 anatomical areas. Thickness is rated from 0-3 (0=normal; 1=mildly increased skin thickness; 2=moderately increased skin thickness; 3=severely increased skin thickness). The scores from each area are then totalled to give a score out of 51 (Khanna et al., 2017).

Change in LoSCAT score	Fage et al. 2018	5	Direct	C	The LoSCAT[5] score has been developed and validated specifically for use in morphoea and is recommended for assessing disease activity in both adults and children (Knobler et al., 2017, Kreuter et al., 2016). Clinically significant improvements are indicated by decreases in activity scores of at least 2 points and/or decreases in damage scores of at least 2 points (Teske and Jacobe, 2019). LoSCAT scores are a useful outcome measure for assessing response to treatment in patients with morphoea because they provide a standard and consistent measure of disease activity at different points in time. Fage et al (2018) measured a complete set of LoSCAT scores in seven patients at baseline and then again after starting treatment (five with generalised disease, one with deep morphoea and one with linear disease). Activity scores improved in five patients (range of improvement 3-15 points, follow-up 3-12 months), worsened in one patient (score increased by 7 points after 16 months) and stayed the same in another (score remained at zero after 18 months follow-up). Damage scores improved in three patients (range of improvement 1-2 points, follow-up 9-25 months), stayed the same in one (follow-up 3 months) and worsened in three others (follow-up 7-12 months). In these seven patients, clinically relevant improvements in activity scores were therefore seen in five patients started on abatacept (four with generalised disease and one with deep morphoea). Clinically relevant improvements in damage scores were seen in two patients (both with generalised disease). The limitations relating to this study and the limitations common to most case series are discussed in 'Changes in mRSS'.
Change in lesion size	Fage et al. 2018	5	Direct	C	Size of skin lesions is an important outcome measure in patients with morphoea because it provides information on the extent of disease. However, it is unclear by exactly how much the lesion would need to reduce in size to confer a clinical benefit to patients. Fage et al. (2018) measured the size of skin lesions in two patients with linear morphoea (morphoea en coup de sabre). There is no mention of how these lesions were chosen or how many other lesions each patient had. Measurements were taken at two points in time; at baseline and after treatment with abatacept. The first patient had a reduction in one lesion from 50.4 cm^2 to 26.6 cm^2 (47% decrease) and another lesion from 52.5 cm^2 to 20.5 cm^2 (61% decrease) after 3-months follow-up. The other patient had a reduction in lesion size from 41.4 cm^2 to 24 cm^2 (42% decrease) after 21-months follow-up. The limitations relating to this study and the limitations common to most case series are discussed in 'Changes in mRSS'. Further to these, measuring the size of skin lesions may not be a reliable way of monitoring response to treatment. For example, the measured size could vary between outcome assessors and could be dependent on the part of the lesion measured.
Reduction in steroid or DMARD use	Adeeb et al. 2017	4	Direct and indirect	C	Reducing the need for steroids or DMARD therapy is an important outcome measure for patients with morphoea because they can be associated with serious treatment side-effects, complications and the need for monitoring. Adeeb et al. (2017) (n=3) reported the case of one patient with mixed localised and linear disease who was commenced on abatacept alongside her current treatment of methotrexate 15mg weekly and prednisolone 10mg daily. Over the course of six months, the patient was able to reduce her dose of prednisolone to 5mg daily and maintain the same dose of methotrexate. The outcomes of two further patients treated with abatacept for severe morphoea were reported in this study. However, these patients

[5] The Localised Scleroderma Cutaneous Assessment Tool (LoSCAT) combines the modified Localised Scleroderma Skin Severity Index (mLoSSI), which assesses cutaneous activity (erythema, thickness and new lesion/lesion extension), the Localised Scleroderma Skin Damage Index (LoSDI) which assesses damage (dermal atrophy, subcutaneous atrophy and dyspigmentation), and the Physician's Global Assessment (PGA) tool (Foeldvari, 2019, Kelsey and Torok, 2013). Both the mLoSSI and the LoSDI have been shown to have good reliability and validity in morphoea studies (Kelsey and Torok, 2013, Fett and Werth, 2011b).

	Stausbol-Gron et al. 2011	2	Direct		were started on abatacept first line, meaning that they did not meet the PICO criteria. The associated evidence is therefore only indirectly applicable to the population of interest. The first patient had deep morphoea and was started on low dose (5mg/day) prednisolone with abatacept, but no information was provided about ongoing steroid use at follow-up. The second patient (with severe generalised morphoea), was started on 60mg prednisolone with abatacept. Over a period of three months, this was gradually tapered to a 10mg daily maintenance dose. This study has some limitations. No details were given about the methods for patient selection (or inclusion/exclusion criteria), and no specified time interval for patient recruitment is stated. This raises the possibility of selection bias. The sample size was very small. . A comparator group of patients who did not receive abatacept was not included. Without a comparator group, it is possible that any changes observed during abatacept treatment could be related to the natural history of the disease or to the concurrent use of steroids. The limitations common to most case series (discussed in 'Changes in mRSS') apply to this study. Follow-up was for 18 months and therefore no conclusions about effectiveness beyond this time can be drawn.
Mobility	Adeeb et al. 2017	4	Indirect	C	Morphoea can affect mobility due to joint pain, restricted joint movement, limb shortening, asymmetry or contractures. This can significantly impact on quality of life and can place added burden on other health and social care services. Improvements in mobility are therefore an important outcome measure when considering the effectiveness of treatment. Adeeb et al (2017) presented three adult patients with morphoea who were treated with abatacept. One of these patients was diagnosed with severe generalised disease with deep tissue involvement using skin biopsy and MRI. At presentation, she was found to have 300 flexion contractures of her knees and absent ankle/foot movements. As a result, she could only walk with assistance. Due to her unusually severe presentation and lack of effective treatment options, she was started on abatacept first line, along with a tapering dose of prednisolone, pregabalin for pain and fexofenadine for itch. After 6-months of treatment with abatacept, she was reported to have significant improvements in her mobility and was able to walk independently due to the resolution of her knee contractures. This patient was started on abatacept as first line treatment for morphoea and therefore could not be deemed to have 'active disease despite treatment with current standard of care'. Despite not strictly meeting the PICO criteria, the outcomes in this patient have been included because they meet the severe clinical disease phenotype. This makes the findings highly relevant to patients with severe disease. However, the associated evidence should be seen as indirectly applicable to the population of interest. Limitations for this study are discussed in 'Reduction in steroid or DMARD use' above. The limitations common to most case series (discussed in 'Changes in mRSS') apply to this study There are some further uncertainties relating to the evidence for this outcome. Because this patient started abatacept first line, it is unclear whether other treatments would have had a similar effect. In addition, the patient received prednisolone (which is a recognised treatment for morphoea), and pregabalin (for pain) alongside abatacept. These could have had a positive impact on mobility, making it difficult to know whether the improvements seen were solely due to abatacept. Lastly, the evidence also relates to only one patient, increasing the risk that the outcomes could have been due to chance, and reducing the reliability of the findings.
MRI changes	Adeeb et al. 2017	4	Indirect	C	MRI scanning can provide an objective measure of depth and breadth of involvement as well as inflammation, sclerosis and atrophy in morphoea (Asano et al., 2018, Florez-Pollack et al., 2018, Shahidi-Dadras et al., 2018). Changes seen on MRI can therefore be a useful outcome measure for monitoring the response to therapy, especially when clinical examination is limited due to the depth of disease (Asano et al., 2018, Florez-Pollack et al., 2018, Shahidi-Dadras et al., 2018).

					Adeeb et al. (2017) conducted whole body MRI in a 55-year-old woman with severe generalised morphoea with deep tissue involvemnt. However, this patient did not meet the PICO criteria for this review because she started abatacept first line. The associated evidence is therefore only indirectly applicable to the population of interest. MRI was performed at baseline, and then again after 6 months of treatment with abatacept. The authors reported that the follow-up MRI demonstrated a 'significant interval treatment response'. They noted a 'decrease in skin and subcutaneous soft tissue hyperintensity and skin thickening, a general reduction in fasciitis and complete resolution of gluteal intramuscular oedema'. However, there was some remaining fascial and skin thickening. The improvements on MRI are reported as striking. It is not clear how these results alone translate into clinical improvements for the patient, but the descriptive outcomes suggest that the patient's signs and symptoms also dramatically improved over the same timescale, and the patient could walk independently without the need for any walking aids (due to resolution of contractures). The use of an MRI scan in this study provides objective evidence of physiological improvements in morphoea with abatacept treatment. However, this patient started abatacept first line. It is therefore not clear whether other (more established) treatments would have had a similar effect. Limitations for this study are discussed in 'Reduction in steroid or DMARD use' above The limitations common to most case series (discussed in 'Changes in mRSS') apply to this study. Only one of the three patients in this case series had an MRI scan, increasing the risk that the outcomes could have been due to chance, and reducing the reliability of the findings. Follow-up was for only 6 months. No conclusions about effectiveness beyond these timescales can be drawn
Visual analogue scales (VAS)	Adeeb et al. 2017	4	Indirect	C	A visual analogue scale is a way of measuring opinions and/ or symptoms across a continuum of values. They are important outcome measures because they capture the opinions and experiences of both the patient and clinicians. Five different VAS scores were recorded in one study providing a standardised measure of disease activity and pain. Adeeb et al. (2017) recorded VAS scores at baseline and then again at 6 and 18-months in one patient (a 55-year-old woman) with severe generalised disease and deep tissue involvement. This patient did not meet the PICO criteria for this review because she started abatacept first line. The associated evidence is therefore only indirectly applicable to the population of interest. Improvements in all scores were noted after 6 months of treatment (50%, 60%, 82%, 66% and 80% respectively). This improvement continued over the next year, and by 18 months all scores had reduced by either 88% (PGP and PDP) or 100% (PGDA, PNP and PhGDA) compared to baseline. Limitations for this study are discussed in 'Reduction in steroid or DMARD use' above The limitations common to most case series (discussed in 'Changes in mRSS') apply to this study. The evidence also relates to only one patient, increasing the risk that the outcomes could have been due to chance, and reducing the reliability of the findings. Because this patient started abatacept first line, it is unclear whether other treatments would have had a similar effect..
Descriptive outcomes	Fage et al. 2018	5	Direct	B	Descriptive outcomes enable clinicians to record their observations in relation to clinical findings that might not otherwise be captured by formal scoring systems or other outcome measures. They provide insight into the patient and/or physician perspective and often give depth to the quantitative data. Fage et al. (2018) state that five of the thirteen patients in their study reported a 'good effect' from treatment (four with generalised morphoea and one with deep disease). One patient described softening of skin and another described a reduction in skin, muscle
	Adeeb et al. 2017	4	Direct and Indirect		

	Stausbol-Gron et al. 2011	2	Direct		and joint symptoms as well as improvements in general wellbeing. One further patient with morphoea en coupe de sabre also described regrowth of hair. No comments were recorded from the remaining seven patients. The limitations relating to this study and the limitations common to most case series are discussed in 'Changes in mRSS'. Although these descriptive outcomes are useful, there is no information about how this data was collected. In addition, only minimal information is given for two of the patients – the authors simply state "good effect according to patient". The authors also do not present any descriptive information about the experiences of seven of the study patients. This outcome measure could therefore be open to reporting bias (only the patients expressing positive views may have been asked about their opinion or only their views were recorded).
Adverse events	Fage et al. 2018	5	Direc	B	It is important to understand the rate and type of adverse events and/or side-effects related to abatacept so that patients and clinicians can be fully informed before use. Fage et al. (2018) recorded adverse events and side-effects experienced by patients during abatacept treatment. Of the thirteen patients included in the study, one patient was diagnosed with ulcerative colitis, meaning that the drug had to be stopped. The authors state that this patient had gastro-intestinal symptoms prior to starting abatacept, and that there was a family history of disease. In total, nine people are recorded as experiencing possible side-effects: • Oral ulcers (n=1) • Sore throat (n=1) • Fatigue (n=3) • Myalgia (n=2) • Diarrhoea (n=1) • Hypertension (n=1) • Headache (n=1) • Herpes labialis (n=1) • Sensations of progressive tightening of the skin and tingling (1) • Nausea/vomiting (n=1) Of these, only one patient stopped treatment with abatacept due to side-effects. This information provides an indication of the number, rate and description of adverse events and/or side-effects that might be associated with abatacept. However, the sample size is small meaning that the results are not necessarily generalisable to the general population with morphoea. In addition, there is no information about how this data was collected, meaning that it may be incomplete. The authors report that five patients had stopped treatment at the study end-point. However, the reason for stopping treatment was not given for two of these five patients. Finally, without a comparator group, it is possible that any symptoms observed during abatacept treatment could be coincidental or related to other factors rather than to the treatment itself. No details were provided about comorbidities or concurrent treatments in the included patients, which could have affected these results.
	Adeeb et al. 2017	4	Direct and Indirect		
	Stausbol-Gron et al. 2011	2	Direct		

9. PICO used in the literature Search

PICO Table	
P – Patients / Population Which patients or populations of patients are we interested in? How can they be best described? Are there subgroups that need to be considered?	Patients **over 2 years** with[6]: Progressive, severe disabling forms of morphoea (localised scleroderma) - generalised, pansclerotic or linear subtypes – where there is active disease despite treatment with current standard of care (For information: 'Severe' refers to disease which: • Causes significant asymmetry or limbs, head and neck OR • Crosses joints and limits mobility OR • Involves 3 sites or is circumferential or involves deep structures OR Functional impairment and/or psychological deterioration might indicate 'Progressive disease'. Current standard treatment consists of topical therapies, phototherapy and systemic therapies including, steroids, methotrexate, mycophenolate mofetil, cyclosporine and/or hydroxychloroquine). Combinations of these may be used.
I – Intervention Which intervention, treatment or approach should be used?	Abatacept alone or in combination with standard systemic therapies IV or subcutaneous administration
C – Comparison What is/are the main alternative/s to compare with the intervention being considered?	Current standard treatment and no abatacept
O – Outcomes What is really important for the patient? Which outcomes should be considered? Examples include intermediate or short-term outcomes; mortality; morbidity and quality of life; treatment complications; adverse effects; rates of relapse; late morbidity and re-admission; return to work, physical and social functioning, resource use.	Efficacy (short and long-term outcomes) demonstrated in stabilisation or improvement in Critical to decision-making a. Clinical severity as measured by e.g. LoSCAT score, and its components (mLOSSI, PGA, LOSDI) and/or modified Rodnan Skin Score b. Quality of life as measured by DLQI (cDLQI as paediatric equivalent) or SF36 c. Function - Mobility, Activities of daily living (ADLs)

[6] In accordance with abatacept licence, available at: https://www.medicines.org.uk/emc/product/2877/smpc

	Important to decision-making d. HADs e. Disease activity/extent on imaging (US/MRI) f. Growth in children g. Number of hospital admissions or re-admissions, length of hospital stay h. Steroid use i. Opportunistic infection j. Requirement for reconstructive surgeries Safety a. Adverse effects b. Toxicity Cost effectiveness

Assumptions / limits applied to search

Inclusions

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:	Over 2 years
Date limits:	2009– 2019

Exclusions

Publication Type:	Conference abstracts, narrative reviews, commentaries, letters and editorials
Study design:	Case reports, resource utilisation studies

10. Search Strategy

Searcher: Rachel Gledhill (Learning and Research Support Librarian, Public Health England)
Date of request: 20/12/2019 **Date results sent:** 31/12/2019
Search question:
What literature is available on Abatacept for severe treatment resistant morphoea (localised scleroderma)?

Key search terms:

Concept 1	Concept 2
Abatacept	Morphoea Morphea Localised scleroderma Localized scleroderma

Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) <1946 to December 27, 2019>

1 Abatacept/ or abatacept.mp. (3605)

2 Scleroderma, Localized/ (4314)

3 morph?ea.ti,ab,kw. (1672)

4 locali?ed scleroderma.ti,ab,kw. (939)

5 2 or 3 or 4 (5106)

6 1 and 5 (4)

Embase <1996 to 2019 Week 52>

1 Abatacept/ or abatacept.mp. (8964)

2 Scleroderma, Localized/ (642)

3 morph?ea.ti,ab,kw. (1872)

4 locali?ed scleroderma.ti,ab,kw. (1162)

5 2 or 3 or 4 (2717)

6 1 and 5 (24)

British Nursing Index

abatacept AND (morphoea or morphea or "localised scleroderma" or "localized scleroderma"). 2 results

CINAHL Complete

abatacept AND (morphoea or morphea or "localised scleroderma" or "localized scleroderma"). 1 result

Health Research Premium Collection

abatacept AND (morphoea or morphea or "localised scleroderma" or "localized scleroderma"). 61 results

Scopus

abatacept AND (morphoea or morphea or "localised scleroderma" or "localized scleroderma"). 15 results

Also searched:

- AMED, Cochrane Database of Systematic Reviews - 0 results for Abatacept.
- Scottish Intercollegiate Guidelines Network (SIGN), National Institute for Health and Care Excellence (NICE) guidelines, Clinical Knowledge Summaries (CKS) guidelines and Primary Care Dermatology Society (PCDS) guidelines - 0 relevant guidelines identified.
- Reference lists of all relevant papers – no new results identified.

Limits applied:
Date: 2010-2019

Summary of resources searched and results:

Source	Number of results
Medline	4
Embase	24
British Nursing Index	2
CINAHL Complete	1
Health Research Premium Collection	61
Cochrane Database of Systematic Reviews	0
Scopus	15
BMJ Best Practice	1
AMED	0
NICE, SIGN, CKS and PCDS guidelines	0

Total number of results after de-duplication: 72

11. Evidence selection

- Total number of publications reviewed: 72
- Total number of publications considered relevant: 14
- Total number of publications selected for inclusion in this briefing: 3

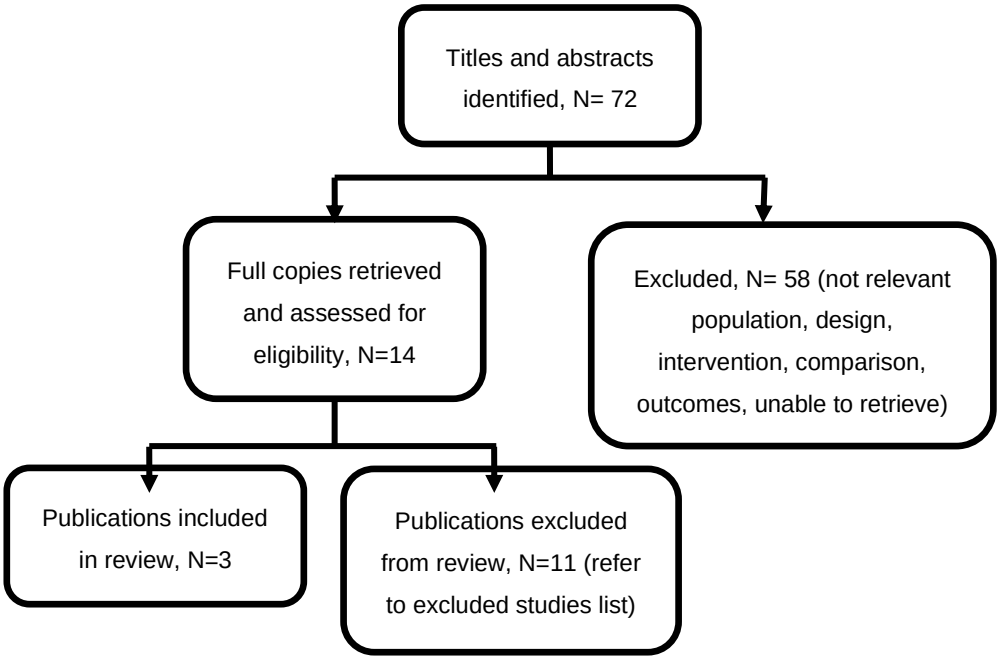

Figure 1: Process of selecting evidence to be included in this review.

	Publication	Reason excluded
1	*Constantin, T., Foeldvari, I., Pain, C. E., et al.* 2018. Development of minimum standards of care for juvenile localized scleroderma. European Journal of Pediatrics 177(7) 961-977	Narrative review
2	*Foeldvari, I.* 2019. Update on the Systemic Treatment of Pediatric Localized Scleroderma. Paediatric drugs 21(6) 461-467	Narrative review
3	*Kreuter, A., Krieg, T., Worm, M., et al.* 2016. German guidelines for the diagnosis and therapy of localized scleroderma. JDDG - Journal of the German Society of Dermatology 14(2) 199-216	Narrative review
4	*Knopfel, N., Luchsinger, I., Schwieger-Briel, A., et al.* 2019. Successful treatment of childhood localized scleroderma with abatacept: A case series. Pediatric Dermatology 36(Supplement 1) S44	Abstract only
5	*Anonymous* 2018. Abatacept: Various toxicities: 9 case report. Reactions Weekly(1703) 14	Duplicate report of findings from the paper by Fage et al (included in this review)
6	*Khan, M. U., Adeeb, F., Devlin, J., et al*. 2018. Abatacept, a promising treatment for early and late-stage morphea subtypes: A follow-up study from the midwest of Ireland. Rheumatology (United Kingdom) 57(Supplement 3)	Abstract only
7	*Lythgoe, H., Almeida, B., Bennett, J., et al.* 2018. Multi-centre national audit of juvenile localised scleroderma: describing current UK practice in disease assessment and management. Pediatric Rheumatology 16	Did not meet the PICO criteria. Audit of current practice.
8	*Wehner Fage, S., Bakke Arvesen, K. & Olesen, A. B.* 2018. Is abatacept a usefull treatment for patients with localized scleroderma? A case description of all localized scleroderma patients treated with abatacept at the department of dermatology, aarhus university hospital, from 2009 to 2016. Journal of Scleroderma and Related Disorders 3(Supplement 1) 243	Abstract only. Duplicate report of findings from the paper by Fage et al (included in this review)
9	*McCarthy, S., Roche, L., Griffin, L., et al*. 2017. Abatacept: A novel treatment in severe limited scleroderma and morphoea. British Journal of Dermatology 177(Supplement 1) 63	Poster abstract
10	*Adeeb, F., Anjum, S., Hussein, O., et al*. 2015. Resolution of generalized deep variant morphea (Morphea Profunda): A case series of three patients successfully treated with abatacept. Annals of the Rheumatic Diseases 74(SUPPL. 2)	Abstract only. Appears to be a duplicate report of findings from the paper by Adeeb et al (included in this review)
11	*Huizinga, T. M. D., Nigrovic, P. M. D., Ruderman, E. M. D., et al*. 2011. Clinical Reviews. International Journal of Advances in Rheumatology 9(4) 139-153	Abstract. Did not meet the PICO criteria - patient population had rheumatoid arthritis (not morphoea)

Table 1: Table showing the papers that were reviewed as full text, but not included in the review, with reasons.

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