CLINICAL PRIORITIES ADVISORY GROUP
10 May 2021

Agenda Item No	5.1
National Programme	Internal Medicine
Clinical Reference Group	Specialised Rheumatology and Specialised Dermatology
URN	1921

Title
Clinical Commissioning Policy Statement Abatacept for treatment of severe treatment-resistant morphoea (localised scleroderma) (adults and children 2 years and over)

Actions Requested	1. Support the adoption of the policy proposition
	2. Recommend its approval as an IYSD.

Proposition
For routine commissioning for patients (adults and children 2 years and over) with severe, treatment resistant morphoea within the criteria set out in this policy statement. Morphoea (localised scleroderma) is an inflammatory disorder that causes sclerotic changes in the skin and soft tissues. It may be limited to skin and subcutaneous tissues, but in severe cases may affect deeper tissues including the muscular fascia, muscles, tendons, joints and bone. Depending on the sub type this can cause significant limb length and bone asymmetry, flexion contractures and impaired mobility, scarring alopecia, ocular and dental problems and neurological complications. These apply to both juvenile onset and adult forms of morphoea. The proposition offers further treatment options for those who have severe disease and are not responding to treatment.

Clinical Panel recommendation
The Clinical Panel recommended that the policy progress as a routine commissioning statement.

The committee is asked to receive the following assurance:	
1.	The Head of Clinical Effectiveness confirms the proposal has completed the appropriate sequence of governance steps and includes an: Evidence Review; Clinical Panel Report and additional PHE evidence report.
2.	The Head of Acute Programmes confirms the proposition is supported by an: Impact Assessment; Engagement Report; Equality and Health Inequalities Impact Assessment; Clinical Policy Proposition. The relevant National Programme of Care has approved these reports.
3.	The Director of Finance (Specialised Commissioning) confirms that the impact assessment has reasonably estimated a) the incremental cost and b) the budget impact of the proposal.
4.	The Clinical Programmes Director (Specialised Commissioning) confirms that the service and operational impacts have been completed.

The following documents are included (others available on request):	
1.	Clinical Policy Proposition
2.	Engagement Report
3.	Evidence Summary plus Public Health additional evidence report.
4.	Clinical Panel Report
5.	Equality and Health Inequalities Impact Assessment

No	Metric	Summary from evidence review
1.	Survival	No evidence available.
2.	Progression free survival	No evidence available.
3.	Mobility	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 30^0 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. 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 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. 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. 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.

4.	Self-care	No evidence available.
5.	Usual activities	No evidence available.
6.	Pain	A visual analogue scale (VAS) 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 morphoea and deep tissue involvement. This patient was started on abatacept first line (due to the extreme severity of disease and lack of effective treatment options), meaning that the associated evidence is indirectly applicable to the population of interest (as discussed in box 3 in the preceding table). Improvements in all scores (Patient Global Disease Activity (PGDA), Patient Global Pain (PGP), Patient Day Pain (PDP), Patient Night Pain (PNP) and Physician Global Disease Activity (PhGDA)) 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. The limitations relating to this study and the limitations common to most case series are discussed in box 3 above. 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.
7.	Anxiety / Depression	No evidence available.
8.	Replacement of more toxic treatment	Reducing the need for steroids or disease modifying anti-rheumatic drugs (DMARDs) 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) 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 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. The limitations relating to this study and the limitations common to most case series are discussed in box 3 above. Follow-up was for 18 months and therefore no conclusions about effectiveness beyond this time can be drawn.
9.	Dependency on care giver / supporting independence	No evidence available.
10.	Safety	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 the disease. This makes it highly unlikely that this was related to abatacept treatment. In total, nine people are recorded as experiencing possible side-effects: • Oral ulcers (1 person) • Sore throat (1 person) • Fatigue (3 people) • Myalgia (2 people) • Diarrhoea (1 person) • Hypertension (1 person) • Headache (1 person) • Herpes labialis (1 person) • Sense of tightening of the skin and tingling (1 person)

		• Nausea/vomiting (1 person) Of these, one patient stopped treatment due to side-effects. This information provides an indication of the rate and seriousness 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.
11.	Delivery of intervention	No evidence available.

No	Metric	Summary from evidence review
1.	Changes in mRSS	The modified Rodnan Skin Score (mRSS) is a measure of skin thickness often used as an outcome measure in *systemic* sclerosis[1]. Clinically meaningful changes in systemic sclerosis correlate with an mRSS score change of 3-4 points. It is an important outcome measure in morphoea because it can provide an indication of the degree and extent of skin disease (and is commonly used in clinical practice). However, the tool was developed and validated for use in systemic sclerosis and has not been validated for evaluating outcomes in morphoea. Fage et al. (2018), reported the 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

[1] MRSS 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

		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 limitations common to most case series (discussed in box 3 in the table above) apply to this study.
2	Change in LoSCAT score	The Localised Scleroderma Cutaneous Assessment Tool (LoSCAT)[2] score has been developed and validated specifically for use in morphoea and is recommended for assessing disease activity in both adults and children. 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. 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 are discussed in box 1 above and the limitations common to most case series are discussed in box 3 in the preceding table.

[2] The 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.

3.	Change in lesion size	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 are discussed in box 1 above and the limitations common to most case series are discussed in box 3 in the preceding table. 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.
4	Descriptive outcomes	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 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 are discussed in box 1 above and the limitations common to most case series are discussed in box 3 in the preceding table. Although these descriptive outcomes are useful, there is no information about how this data was collected. In addition, the authors 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).
5	MRI changes	MRI scanning can provide an objective measure of depth and breadth of involvement as well as inflammation, sclerosis and atrophy in morphoea. 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. Adeeb et al. (2017) conducted whole body MRI in a 55-year-old woman with severe generalised morphoea with deep tissue involvement. 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. The limitations relating to this study and the limitations common to most case series are discussed in box 3 in the preceding table. 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.

Patient Impact Summary

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

- **mobility:** Patients with linear disease of the leg(s) or pansclerotic morphoea have moderate to severe problems in walking about.
- **ability to provide self-care:** Patients have moderate to severe problems in washing or dressing.
- **undertaking usual activities:** Patients have severe problems in doing their usual activities and in the most severe cases are unable to do their daily activities.
- **experience of pain/discomfort:** Patients have moderate pain or discomfort.
- **experience of anxiety/depression:** Patients are often/extremely anxious or depressed.

Further details of impact upon patients:

Pansclerotic morphoea causes itching, burning pain, restriction of chest expansion, affecting breathing and reduced movement across multiple joints. Patients mobility is severely impaired, and they become wheelchair users. They may have to change living/ working arrangements and become unemployed. This can happen rapidly and cause a significant impact on mental health. Linear disease causes limb and face asymmetry. It impacts limb growth in children and muscle bulk in adults, affecting physical appearance, mobility and exercise capacity. Patients can experience intense anxiety, depression and in extreme cases, suicidal thoughts**.** Patients can face a significant financial impact.

Further details of impact upon carers: Patients can become dependent on carers as the disease progress. Carers cope with the pain and emotional distress of their partner or child. They may have to wash, clothe & feed them. They support children who may be bullied or have difficulties at school. Carers often give up work.

Considerations from review by Rare Disease Advisory Group

Not applicable.

Pharmaceutical considerations

The clinical commissioning policy proposition recommends abatacept for treatment of severe treatment-resistant morphoea (localised scleroderma) in adults and children 2 years and over. This is an off-label use of the medicine which is excluded from tariff.

Considerations from review by National Programme of Care

1) The NPoC noted the significant impact on patients of severe morphoea disease which is the focus of this policy proposition. The proposition received the full support of the Internal Medicine NPoC Assurance Group in November 2020.