Clinical Commissioning Policy Statement
Abatacept for treatment of severe treatment-resistant morphoea (localised scleroderma) (adults and children 2 years and over) (210505P) [1921]

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Commissioning position

Summary

Abatacept is recommended as a treatment option through routine commissioning for patients (adults and children 2 years and over) with severe, treatment resistant morphoea within the criteria set out in this document.

Information about abatacept

The intervention

Abatacept belongs to a group of medicines called biological therapies. It is a protein which interrupts the interaction between T cells, a type of white blood cell involved in inflammation, and the other immune cells which activate these T cells. This results in decreased T cell activation, and therefore decreased inflammation, a key process of the disease activity in morphoea (localised scleroderma). Abatacept is currently widely used for rheumatoid arthritis as an approved biologic treatment. It may be administered intravenously or subcutaneously, self-injected by competent patients or their carers following their initial dose. Some patients with severe disease may require initial intravenous loading dose(s). A majority of patients will receive the treatment as subcutaneous injections.

Committee discussion

Clinical Panel acknowledged the evidence base was limited but considered the proposition reflected the available evidence.

See the committee papers (link) for full details of the evidence.

The condition

Morphoea (localised scleroderma) is an idiopathic inflammatory disorder that causes sclerotic changes in the skin and soft tissues. Whilst typically limited to skin and subcutaneous tissues, it may affect deeper tissues including the muscular fascia, muscles, tendons, joints and bone. Although the exact trigger and disease process is not fully understood, it is thought that excessive T cell activation plays a key role. This leads to increased release of pro-inflammatory and pro-fibrotic mediators ultimately leading to increased collagen deposition.

The term morphoea covers a wide spectrum of clinical manifestations, which varies significantly in terms of its severity, depending on the extent, depth of involvement and activity of disease. Subtypes include a limited form of morphoea, a disseminated plaque form, a pansclerotic form and linear morphoea. There is no formal published definition of severe disease although it is widely agreed that it is based on site, extent, depth of involvement and potential to develop

damage including functional and psychological impairment (Li et al., 2012, Orteu, 2016). Specifically, sub-types with disease crossing joints, thus limiting mobility and those occurring at multiple body sites (greater than 3 sites) or circumferentially constitute the severe phenotype. Patients with severe disease of deep disseminated plaque, pansclerotic and linear subtypes are the focus of this policy statement. Whilst all sub-types described above can have superficial or deep involvement, the linear and pansclerotic forms are the most likely to involve structures below the skin such as fascia, muscle and bone and require systemic therapies (Knobler 2017, Orteu 2016, Albuquerque 2019). Linear disease can cause significant limb length and girth asymmetry, flexion contractures and impaired mobility. Linear head and neck disease can cause facial asymmetry, scarring alopecia, ocular and dental problems and neurological complications including migraine and epilepsy. These apply to both juvenile onset and adult forms of morphoea.

The age and sex adjusted incidence for morphoea (localised scleroderma) is 27/million/year overall and 5/million/year for linear disease (Peterson et al. 1997). In a study of UK and Irish children the reported incidence of morphoea was 3.4/million children (<16years) per year, and 2.5/million/year for linear disease (Herrick et al. 2010). Pansclerotic morphoea is rare, accounting for 3.6% of a US cohort of 360 morphoea patients and 7% of a cohort of 261 adult morphoea patients seen in the Royal Free Dermatology connective tissue disease service (unpublished observation).

Current treatments

There is limited high quality research available to guide treatment decisions in these patients. Standard therapies for milder forms of morphoea (localised scleroderma) include topical treatments such as corticosteroids, calcineurin inhibitors, calcipotriol as well as phototherapy This policy statement relates to patients with severe localised scleroderma, a very small cohort within an already rare disease. In patients with severe skin and/or musculoskeletal involvement, systemic therapies are used. Currently, in individuals resistant to standard therapies available options are combination therapies with methotrexate, mycophenolate, ciclosporin, prednisolone and/or hydroxychloroquine, with increasing potential for drug induced complications. Reconstructive or corrective surgeries may be required.

Comparators

Treatment with topical and systemic therapies. Topical treatments include corticosteroids, calcineurin inhibitors, calcipotriol and phototherapy. Systemic therapy includes oral and IV corticosteroids as well as conventional DMARDs such as methotrexate, mycophenolate mofetil, cyclosporin and hydroxychloroquine.

Evidence summary

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 evidence population (PICO) 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 that 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.

Implementation

Criteria

Patients must meet all of the following inclusion criteria to be considered for treatment with abatacept:

- Patients **2 years of age and over** with severe disabling forms of morphoea (localised scleroderma) – disseminated plaque, pansclerotic or linear subtypes. Severe disease is defined as:
  - Disease crossing joints and limiting mobility AND/OR
  - Occurring at multiple body sites (3 or more) or circumferentially AND/OR
  - Involving the deeper structures including fascia, muscle or bone
- Progressive disease course with functional impairment and/or psychological deterioration (as assessed with Hospital Anxiety and Depression Scale (HADS))
- Non-response*/intolerance to current standard treatment which may include topical therapies, phototherapy and oral therapies including corticosteroids and at least two of the following DMARDs: methotrexate, mycophenolate mofetil, ciclosporin, hydroxychloroquine.

*Non-response as assessed by LoSCAT and/or mRSS at affected sites, physician's global assessment of activity (PGA-A) and physician's subjective assessment of improvement (PSAI).

Exclusion criteria

Patients with any of the following should not be treated with abatacept:

- Known active, current or significant history of recurrent bacterial, viral, fungal, mycobacterial, or other infections (including but not limited to tuberculosis (TB) and atypical mycobacterial disease, hepatitis B and C, and herpes zoster, but excluding fungal infections of the nail beds),

Dose

Adults
Induction

In severe cases intravenous induction doses will be given at a dose of 500-1000mg (weight dependent, as per Summary of Product Characteristics) at baseline, weeks 2 and 4.

Maintenance

Subcutaneous injection 125mg weekly. If the subcutaneous route is not suitable, patients can be given intravenous abatacept for maintenance.

Children

Intravenous abatacept may be used during induction (3 doses at day 0, 14, and 28) using Summary of Product Characteristics (SPC) doses followed by weekly subcutaneous injection guided by weight (Table below). Intravenous treatment may be continued in children who cannot tolerate weekly subcutaneous injections (Kalampokis et al 2020).

INTRAVENOUS dose

The recommended dose of abatacept for patients 6 to 17 years of age who weigh less than 75kg is 10 mg/kg calculated based on the patient's body weight at each administration. Paediatric patients weighing 75kg or more should be administered abatacept following the adult dosing regimen, not to exceed a maximum dose of 1000mg.

The safety and efficacy of intravenous Abatacept in children below 6 years of age have not been studied and therefore, intravenous Abatacept is not recommended for use in children under six years old.

SUBCUTANEOUS dose

The recommended weekly dose of Abatacept solution for injection in pre-filled syringe for patients 2 to 17 years of age is:

Body weight (kg)	Weekly Dose
10kg to less than 25kg	50mg
25kg to less than 50kg	87.5mg
50kg or more	125mg

Monitoring

Screening for chronic infections prior to commencement of treatment will be undertaken, including investigations for TB (with chest x-ray or interferon-based test or Mantoux tuberculin skin test), hepatitis B and C with HIV serology, and immunity to VZV will be confirmed. Patients should have a clinical assessment as described in the data collection section, including PSAI HADS, LoSCAT and/or mRSS at any affected sites, and/or PGA-A at baseline, interim assessment at 6 months and formal response assessment at 12 months. Baseline photo documentation of clinical lesions is advisable although this may not be a robust measure of clinical response to Abatacept.

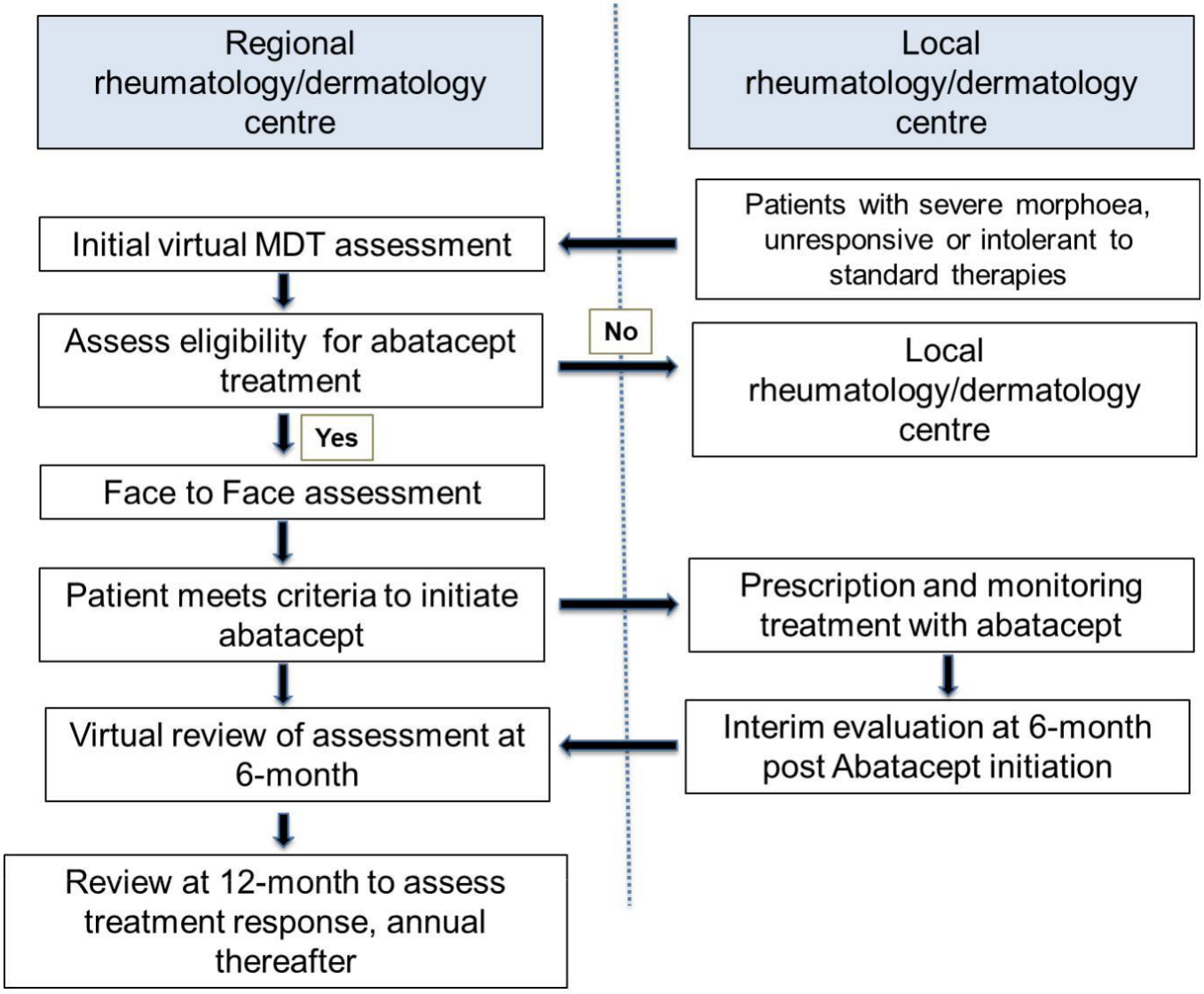
Stopping criteria

There will be a review of response to treatment at 12 months. Treatment should be stopped if the physician's subjective assessment of improvement is worsened from baseline and any one of the following additional criteria are met:

- No or less than 25% improvement in the LoSCAT activity score
- No improvement in the PGA-A
- No improvement in mRSS at any affected sites

Patient pathway

Patients requiring treatment with abatacept will be referred by their usual consultant rheumatologist and/or dermatologist for an initial virtual multi-disciplinary team (MDT) opinion from their regional specialised rheumatology/dermatology centre. The MDT will comprise specialists in rheumatology and dermatology in both adult and where appropriate, paediatric services from regional and referring centres. The regional centre will be either co-located in one centre or across two agreed Trusts and each centre will have a clinical and research interest in scleroderma. Key sites from the UK Scleroderma Study Group (UKSSG) including paediatric centres from Scleroderma Topic Specific Group will be identified to establish a network of services across England. If, after initial assessment the patient is considered eligible for abatacept treatment, a face to face assessment by these regional specialised centres will be arranged. If the agreed commissioning criteria are met, abatacept can be prescribed by the patient's usual dermatology/rheumatology centre, provided they have sufficient experience of use of abatacept. Access to abatacept will follow the online prior approval form system to ensure compliance with the agreed pathway. Interim evaluation of treatment response will take place at the local centre with review at the regional specialised rheumatology/dermatology centre virtual MDT meeting at 6-months. Subsequent annual reviews will be conducted at the regional specialist centres. If the patient meets the criteria for successful response to treatment with 12-month of abatacept, treatment will continue to be prescribed locally.



Effective from
This policy statement is effective from the date of publication.

Mandatory data collection
Baseline clinical outcome data recorded to include:
Subtype and site of morphoea, age at onset of disease, previous treatment history and outcomes, patient reported outcomes and clinician reported outcomes as below.

Follow-up outcome measures recorded should include the baseline measures in addition to: requirement for intravenous induction dose, duration of treatment, dose (for paediatric cases), whether treatment has been discontinued, tolerability and/or adverse local reactions. These data should be recorded in a national audit.

Patient reported outcomes

- Patients' quality of life can be evaluated with the Dermatology Life Quality Index (DLQI) or paediatric equivalent CDLQI
- HADS or paediatric equivalent.

Clinical Outcome measures

- LoSCAT and or/mRSS at any affected sites
- Physician's subjective assessment of improvement (PSAI: Improved, unchanged or worse since last visit).
- Physician's global assessment of activity (PGA-A)

Data will be collected according to the above recommendations at the regional centre at initiation, 6 months and annually thereafter for up to 5 years. An interim assessment should take place at the local centre, with (virtual) MDT meeting review at regional centre at 6 months, to document data on response and safety/tolerability.

Mechanism for funding

The funding and commissioning will be managed through the relevant local NHS England Specialised Commissioning Team.

Policy review date

This is a policy statement, which means that the full process of policy production has been abridged: public consultation has not been undertaken. If a review is needed due to a new evidence base, then a new Preliminary Policy Proposal needs to be submitted by contacting england.CET@nhs.net.

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

Equality Statement

Promoting equality and addressing health inequalities are at the heart of NHS England's values. Throughout the development of the policies and processes cited in this document, we have:

- Given due regard to the need to eliminate discrimination, harassment and victimisation, to advance equality of opportunity, and to foster good relations between people who share a

relevant protected characteristic (as cited under the Equality Act 2010) and those who do not share it; and

- Given regard to the need to reduce inequalities between patients in access to and outcomes from healthcare services and to ensure services are provided in an integrated way where this might reduce health inequalities

Definitions

Term	Definition
DMARD	Disease-modifying antirheumatic drug. Medications used in the management of inflammatory conditions, which generally have immune-suppressive action. Including ciclosporin, hydroxychloroquine, methotrexate, mycophenolate mofetil, sulfasalazine, azathioprine, cyclophosphamide, leflunomide.
LoSCAT	Localised scleroderma assessment tool. This includes both the modified localised scleroderma skin severity index (MLoSSI) and the localised scleroderma skin damage index (LoSDI). 18 anatomical sites are assessed (head, neck, chest, abdomen, upper back, lower back, both upper arms, both forearms, buttocks/thighs, legs and feet). mLOSSI assessed for: new lesions, increase in size of a lesion, erythema (redness) and skin thickness. LOSDI measures: skin thinning, loss of fat under the skin (subcutaneous) and loss/change of normal skin pigmentation (colour).
T cell	White blood cell which forms part of the body's immune system. They work to attack foreign bacteria and other microbes, however at times they can attack the body's own cells. This is termed 'autoimmune'.
Hospital anxiety and depression score (HADS)	A 14-point questionnaire, 7 questions each relating to symptoms of depression and symptoms of anxiety experienced in the last week.
Off-label	Off-label use of a medicine is use outside of its license. A medicine's license states the illness it is approved to treat, as well as the patients it can be given to (e.g. a medicine may be licensed for adults but not children) and the form it should be given in. Licensing is done by the medicine's manufacturer on the basis of clinical trial data. In the case of rare disease, clinical trial data may not be readily available so after careful consideration of available evidence a medicine may be used outside of its license – 'off-label'.

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