CLINICAL PRIORITIES ADVISORY GROUP
10 May 2024

Agenda Item No	2.1
National Programme	Blood and Infection
Clinical Reference Group	Specialised Immunology and Allergy
URN	2309

Title
Abatacept for autoimmune complications of primary immunodeficiencies caused by CTLA-4 or LRBA genetic mutation (aged two years and over)

Actions Requested	1. Support the adoption of the policy proposition
	2. Recommend its relative prioritisation

Proposition
Abatacept is recommended to be available as a routine commissioning treatment option for autoimmune complications of primary immunodeficiencies caused by CTLA-4 or LRBA genetic mutation within the criteria set out in this document. Primary immunodeficiencies (PID) are rare heritable conditions where the body's immune system does not work properly and in some cases attacks itself (autoimmunity). Abatacept is a biological drug that specifically targets T_{Reg} cells. Abatacept is used to maintain remission in this condition. This proposed use of abatacept is off label. The policy proposition is restricted to adults and children aged two years and over in line with licensed indications for abatacept as there is insufficient evidence of safe use of intravenous abatacept in children younger than two. Specialised immunology services are suitable and ready for delegation from April 2025.

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

The committee is asked to receive the following assurance:	
1.	The Deputy Director of Clinical Effectiveness confirms the proposition has completed the appropriate sequence of governance steps and includes an: Evidence Review; Clinical Panel Report.
2.	The Deputy Director 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 Director of Clinical 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
4.	Clinical Panel Report
5.	Equality and Health Inequalities Impact Assessment

In patients with primary immunodeficiencies associated with LRBA or CTLA-4 genetic mutation, what is the clinical effectiveness and safety of abatacept compared with standard care?

Outcome	Evidence statement
Clinical Effectiveness	
Critical outcomes	
Disease remission **Certainty of evidence:** Very low	This outcome is important to patients because the absence of disease remission may indicate that their condition is not adequately controlled by their current treatment, impacting on quality of life, life expectancy and patient treatment decisions. In total, one retrospective case series reported non-comparative evidence relating to disease remission or response in children and adults with LRBA deficiency following treatment with abatacept. Duration of treatment was not reported. **At unspecified duration of follow-up:**

Outcome	Evidence statement
	• One retrospective case series (Tesch et al 2020) (n=14) used a specially developed IDDA score[1] to assess disease burden and treatment responses. A statistically significant improvement in the median IDDA score between before and after treatment with abatacept was reported (median score 34 versus 18.5, p=0.0039). **(VERY LOW)** **One retrospective case series provided very low certainty evidence of a statistically significant improvement in the median score on a specially developed scale reported to assess disease burden and treatment responses at unspecified duration of follow-up in children and adults with LRBA deficiency.**
Organ specific disease activity/response **Certainty of evidence:** Very low	These outcomes are important to patients as objective measures of functioning of affected organs. Given the progressive nature of PID, disease activity results might not be expected to return to normal following treatment, however, stabilisation may indicate treatment has successfully limited disease progression. In total, two case series (one retrospective, one prospective) reported non-comparative evidence relating to organ specific disease activity/response in children and adults with CTLA-4 insufficiency (Egg et al 2022) or children with LRBA deficiency (Kiykim et al 2019). Outcomes were not clearly defined by the studies and one study did not report duration of treatment. Median duration of treatment in Kiykim et al 2019 was 12.5 months (range 5-33 months). **At unspecified duration of follow-up:** • In ten patients with GLILD, Egg et al 2022 observed a full response in *lung disease activity* in 5/10 patients (50%), a partial response in 2/10 patients (20%) and no response in 1/10 (10%). No data were available for 2/10 (20%). **(VERY LOW)** • Two case series reported remission of *gastrointestinal activity*. Egg et al 2022 reported an initial clinical response in 9/9 patients with gastrointestinal involvement, but two patients had a relapse of diarrhoea, giving a response rate of 7/9 (78%). Kiykim et al 2019 reported that among 14 patients with chronic diarrhoea, complete remission of

[1] A specially developed score to assess disease burden and treatment responses that includes an assessment of organ involvement (graded 0-4, depending on the severity and need for treatment), weighted by performance indices and added to the score for days of hospitalization, the need for intensive or supportive care, and the number of infections. Lower values indicate benefit, but the clinical meaning of the values is unclear and the clinical importance of the difference is not reported.

Outcome	Evidence statement
	diarrhoea occurred in 11/14 (78.6%) and partial remission occurred in 3/14 (21.4%) of patients. **(VERY LOW)** • A response (not defined) in *inflammatory nervous system lesions* occurred in 4/6 (66.7%) patients with neurological involvement in Egg et al 2022. **(VERY LOW)** • Two case series reported evidence relating to *haematological remission*. Egg et al 2022 stated that abatacept was reported to be 'helpful' in 3/3 patients with haematological conditions (one with chronic ITP, one with chronic AIHA, one with chronic PRCA). Kiykim et al 2019 reported that among ten patients with lymphoproliferation, complete remission was observed in 80% and partial remission was observed in 10% of patients. Kiykim et al 2019 also reported complete remission of haematological immune dysregulation (AIHA, ITP) in 80% of patients (n not reported). **(VERY LOW)** • In 13 patients with *immune dysregulation symptoms*, Kiykim et al 2019 observed complete remission in five patients (38.5%) and partial remission in four patients (30.8%). **Among** non-haematological immune dysregulatory symptomatologies[2], complete remission occurred in 10% of patients (n not reported). Type 1 diabetes was reported to be not reversible after abatacept in 3 patients. **(VERY LOW)** • **Kiykim et al 2019** stated that in all 18 patients, at least one of the symptoms was completely or partially controlled. **(VERY LOW)** **Two case series (one retrospective and one prospective) provided very low certainty evidence that most children and adults with CTLA-4 insufficiency or children with LRBA deficiency experienced full or partial response or remission of organ specific disease including lung, gastrointestinal, haematological, lymphoproliferative, neurological and immune dysregulation at unspecified duration of follow-up.**
Symptom alleviation **Certainty of evidence:** Very low	This outcome is important to patients because reduction of symptoms directly improves the patient's quality of life. This outcome is both a key indicator of the effectiveness of treatment and provides an insight into the patient's perception of the effectiveness of treatment. In total, two retrospective case series reported non-comparative evidence relating to symptom alleviation in children and adults with LRBA deficiency or CTLA-4

[2] Diabetes, alopecia, arthritis, demyelinating disease, granulomatous-lymphocytic interstitial lung disease.

Outcome	Evidence statement
	insufficiency (Catak et al 2022) or children and adults with LRBA deficiency (Tesch et al 2020). **At mean 6.8 years (SD 8.1 years) follow-up:** • Catak et al 2022 reported that among n=6 patients with CTLA-4-insufficiency, 3/6 showed 'good responses' at the maintenance dose Outcomes were not reported for three of the patients with CTLA-4-insufficiency. **(VERY LOW)** **At unspecified duration of follow-up:** • Catak et al 2022 reported that all patients with LRBA deficiency (n=23) 'showed alleviation in symptoms' (although there was inadequate response in one patient after two years, see under 'Treatment Failure'. **(VERY LOW)** • Tesch et al 2020 reported that among 14 patients with LRBA deficiency treated with abatacept monotherapy, 10/14 (71.4%) were reported to show a good general response with an amelioration of almost all symptoms, 3/14 (21.4%) were reported to show neither a decrease in disease activity in different organ systems nor an amelioration of signs of autoimmunity and immune dysregulation, and in 1/14 (7.1%) only autoimmune cytopenia could be resolved, but lymphoproliferation, parenchymal lung disease, endocrinopathy, failure to thrive, and severe infections were refractory to abatacept. **(VERY LOW)** **Two retrospective case series provided very low certainty evidence that there is improvement in some symptoms following treatment with abatacept, at mean 6.8 years follow-up in children and adults with CTLA-4 insufficiency and at unspecified duration of follow-up in children and adults with LRBA deficiency.**
Important outcomes	
Treatment failure **Certainty of evidence:** Very low	Treatment failure is important to patients as it reflects the effectiveness of the intervention. Consequences of failure to control immunity are associated with significant patient morbidity including ongoing relapses of intractable cytopenias, ongoing progression of granulomatous lung or other organ specific diseases and increasing morbidity and mortality. This would lead to further consideration of HSCT and (for cytopenias) splenectomy. In total, one retrospective case series reported non-comparative evidence relating to treatment failure in children and adults with LRBA deficiency.

Outcome	Evidence statement
	• Catak et al 2022 reported that 1/23 patients (4.4%) stopped treatment due to inadequate response after two years of abatacept treatment. **(VERY LOW)** **One retrospective case series provided very low certainty evidence that treatment failure occurs in 4.4% of children and adults with LRBA deficiency after two years of abatacept treatment.**
Safety	
Adverse events **Certainty of evidence:** Very low	These outcomes are important to patients because they will impact on their treatment choices, recovery and could have long term sequelae if they are irreversible. They reflect the tolerability and adverse effects of the treatment. From a service delivery perspective, they reflect the additional demands placed on the health system to manage the adverse consequences of the treatment. One retrospective case series reported non-comparative evidence relating to adverse events in children and adults with LRBA deficiency. **At 0.1 to 5 years (total 400 patient months) follow-up:** • Tesch et al 2020 (n=23) stated that 0/23 patients had no immunosuppression-associated malignancy, 0/23 had no increase in susceptibility to infections, 2/23 (8.7%) had newly developed eczema, and 21/23 had no side effects after abatacept initiation. **(VERY LOW)** **One retrospective case series provided very low certainty evidence that non-severe adverse events were experienced by very few children and adults with LRBA deficiency treated with abatacept.**
Abbreviations AIHA: autoimmune haemolytic anaemia; ALPS: autoimmune lymphoproliferative syndrome; CTLA-4: cytotoxic T lymphocyte antigen 4; GLILD: granulomatous-lymphocytic interstitial lung disease; IDDA: immune deficiency and dysregulation activity score; ITP: immune thrombocytopenia; LRBA: lipopolysaccharide-responsive beige-like anchor; PRCA: pure red cell aplasia	

In patients with primary immunodeficiencies associated with LRBA or CTLA-4 genetic mutation, what is the cost effectiveness of abatacept compared with standard care?

Outcome	Evidence statement
Cost effectiveness	**No evidence was identified for cost effectiveness**

From the evidence selected, are there any subgroups of patients that may benefit from abatacept more than the wider population of interest?

Subgroups	Evidence statement
Organ specific disease	One prospective case series (Kiykim et al 2019) and one retrospective case series (Egg et al 2022) reported response in organ specific disease including lung, gastrointestinal, haematological, lymphoproliferative, neurological and immune dysregulation. Outcomes were reported as 'response' or 'remission' in organ-specific disease; no organ-specific measures were used. No comparisons in remission or response rates between different organ specific subgroups were reported and there was no evidence as to whether or not any organ specific disease subgroups benefit more from treatment with abatacept
Adults vs children	No evidence was identified for adults versus children

From the evidence selected, what dose of abatacept was used?

Outcome	Evidence statement
Dose of abatacept	Three case series reported the dose of abatacept used. Catak et al 2022 used a maintenance dose of 10-15 mg/kg per month. Kiykim et al 2019 used a dose of 10 to 20 mg/kg every 1 to 4 weeks. Egg et al 2022 used 125 mg per week subcutaneously, sometimes with a loading dose of 500-1000 mg intravenously.

Patient Impact Summary
The condition has the following impacts on the patient's everyday life: • **mobility:** Patients can have significant problems in walking about • **ability to provide self-care:** Patients can have significant problems in washing or dressing • **undertaking usual activities:** Patients can have severe problems in doing their usual activities • **experience of pain/discomfort:** Patients have severe pain or discomfort • **experience of anxiety/depression:** Patients are severely anxious or depressed
Further details of impact upon patients: Patients with CTLA-4 or LRBA deficiency are immunocompromised and therefore at much higher risk of recurrent infections. Patients may spend a long time

recovering from infections, only to be re-infected. This may result in patients having to give up work or stay off school and can have a significantly negative impact on their personal life. In addition to recurrent infections, patients acquire other autoimmune complications, including diabetes, colitis, lung damage or dermatological conditions. All of this can lead to long-term organ damage and increased morbidity.

Further details of impact upon carers:

Those living with and caring for people with PID may find themselves in this role suddenly and it can require a complete upheaval in the way they are living their life. These challenges are only more substantial for carers of people with severe immunocompromise who have to self-isolate and those unable to work who they may have to financially, as well as physically, support.

Considerations from review by Rare Disease Advisory Group
RDAG members commented that there was a very limited evidence base for this indication and welcomed the recommendation to collect more evidence. They acknowledged the difficulty in designing clinical trials for patients with rare diseases but highlighted the importance of using the best evidence possible particularly in the areas of clinical and cost effectiveness. Colleagues from the Northern Ireland commented that they have local commissioning and approval processes for drugs.

Pharmaceutical considerations
This clinical commissioning policy proposition recommends abatacept as a treatment option for autoimmune complications of primary immunodeficiencies caused by CTLA-4 or LRBA genetic mutation, in people aged 2 years and over. The recommendation is outside of the marketing authorisation for abatacept, so use is off-label and Trust policy regarding unlicensed medicines should apply. Abatacept is on the NHS Payment Scheme Annex A, that is, it is an excluded drug. Use in children from the age of 2 years is based on the studies that have informed the policy, which all included children.

Considerations from review by National Programme of Care
The proposal received the full support of the Blood and Infection PoC on the 26th March 2024.