NHS England Evidence Review:

Abatacept for autoimmune complications of primary immunodeficiencies caused by CTLA-4 or LRBA genetic mutation

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Abatacept for autoimmune complications of primary immunodeficiencies caused by CTLA-4 or LRBA genetic mutation

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Contents

1. Introduction

This evidence review examines the clinical effectiveness, safety and cost effectiveness of abatacept compared with current standard care in patients with primary immunodeficiencies (PID) associated with LRBA or CTLA-4 genetic mutation.

PID is a rare heritable condition where the body's immune system does not work properly and in some cases attacks itself. The illness can affect one or many parts of the immune system and the genetic causal mechanisms can vary greatly. One of the presentations of PID is of chronic immune dysregulation which may cause autoimmune disease including chronic inflammation. This may be caused by dysfunction of the regulatory T (T_{Reg}) cell which is essential for preventing autoimmunity. Genetic causes for these immune deficiencies have been identified in some patients, including monogenic deficiency of the LRBA and CTLA-4 genes which are responsible for normal regulation of the T_{Reg} cell.

Patients often suffer with complex autoimmune diseases that may include autoimmune lung disease, a range of skin diseases including psoriasis and vitiligo, arthritis, immune cytopenias, neuro-inflammation, inflammatory bowel disease/enteropathy and granulomatous to fibrotic liver disease. Patients are also vulnerable to infection. The current prevalence of T_{Reg} cell dysfunction based PID in England is estimated to be 60 patients with a new diagnosis of 1 patient per annum.

Abatacept is a biological drug that specifically targets T_{Reg} cells. It is licenced for rheumatoid and psoriatic arthritis in adults and for polyarticular juvenile idiopathic arthritis in children aged two years and older. It can be given intravenously or subcutaneously. Abatacept is proposed to be used long-term to treat the autoimmune or inflammatory complications such as granulomatous inflammatory lung disease, arthritis inflammatory bowel disease and autoimmune cytopenias that arises due to T_{Reg} cell dysfunction. This proposed use of abatacept is off-label.

There is no standard current treatment, and each autoimmune complication of PID tends to be managed in isolation by immunology specialists in tertiary centres. This is usually with steroids, sirolimus, rituximab and non-specific immune suppressant agents, such as azathioprine, mycophenolate mofetil. Definitive treatment for PID is allogeneic hematopoietic stem cell transplant (HSCT), which NHS England currently commissions. Splenectomy may also be considered in intractable cytopenias.

In addition, the review scope included the identification of possible subgroups of patients within the included studies who might benefit from abatacept more than the wider population of interest, and the dose of abatacept that was used.

2. Executive summary of the review

This evidence review examines the clinical effectiveness, safety and cost effectiveness of abatacept compared with standard care for the treatment of patients with primary immunodeficiencies associated with LRBA or CTLA-4 genetic mutation. The searches for evidence published since January 2013 were conducted on 8th August 2023 and identified 756 references. The titles and abstracts were screened and 11 full text papers were obtained and assessed for relevance.

Four studies were identified for inclusion, three retrospective case series and one prospective case series, including between 18 and 29 patients treated with abatacept. Median treatment duration ranged from 12.5 months to 30 months in the two studies that reported this. Two studies were conducted in Turkey and two were multinational studies. No studies comparing abatacept with standard care were identified.

In terms of clinical effectiveness:

- **Disease remission (critical outcome).** 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 (critical outcome).** 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.
- **Symptom alleviation (critical outcome).** 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.
- **Treatment failure (important outcome).** One 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.
- **Radiographic changes (important outcome).** No evidence was identified.
- **Quality of life (important outcome).** No evidence was identified.
- **Steroid use reduction (important outcome).** No evidence was identified.

In terms of safety:

- 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.

In terms of cost effectiveness:

- No evidence was identified for cost effectiveness.

In terms of subgroups:

- There was no evidence as to whether or not any organ specific disease subgroups benefit more from treatment with abatacept. No evidence was identified for subgroups of children and adults.

Limitations

No studies compared the clinical effectiveness or safety of abatacept with standard care. One prospective case series only included patients receiving abatacept; the others were retrospective case series which also included patients receiving other treatments. All of the studies had a high risk of bias and certainty about the evidence for all critical and important outcomes was very low when assessed using modified GRADE. There was heterogeneity between the studies in terms of their populations. One study included children only and three studies included both children and adults, but did not analyse them separately. Two studies included patients with LRBA deficiency only, one study included patients with CTLA-4 insufficiency only, and one study included patients with either genetic mutation. None of the studies clearly reported clinical and demographic information of the participants receiving abatacept treatment, and none clearly indicated that they had consecutive and complete inclusion of participants. The abatacept regimens differed between the studies, and varied between centres in at least one of the studies. Only two studies reported duration of treatment, and only two reported duration of follow-up for some outcomes only. It is unclear whether the patients received additional treatments and whether these were consistent within and between studies. The outcomes were poorly defined and there was missing information in the studies. None of the studies provided evidence for the important outcomes of radiographic changes, quality of life and steroid use reduction. Three studies did not report any information on adverse events, and the fourth study reported only selected information. The studies were small with very few patients from the UK. The overall generalisability of the results to the UK NHS setting is unclear.

Conclusion

The studies identified for this review provide very low certainty evidence for the critical and important outcomes of disease remission, organ specific disease activity/response, symptom alleviation and treatment failure, and one study provided very low certainty evidence on safety. No comparative studies were identified, so no conclusions can be reached about the clinical effectiveness or safety of abatacept compared with standard care. No evidence was identified for the important outcomes of radiographic changes, quality of life or steroid use reduction, and no evidence on cost effectiveness was found. Outcomes were not well defined and information about duration of treatment and any other treatment received was lacking in some studies. However, the available very low certainty evidence suggests that symptom alleviation or full or partial disease remission occurs in most patients with primary immunodeficiencies associated with LRBA or CTLA-4 genetic mutation who were treated with abatacept, including patients with lung, gastrointestinal, haematological, lymphoproliferative, neurological and immune dysregulation. One retrospective case series provided very limited evidence about safety which suggested that that non-severe adverse effects were experienced by very few patients treated with abatacept. The limitations of the studies and lack of comparative data limit the strength of the conclusions that can be drawn.

3. Methodology

Review questions

The review questions for this evidence review are:

1. In patients with primary immunodeficiencies associated with LRBA or CTLA-4 genetic mutation, what is the clinical effectiveness of abatacept compared with standard care?
2. In patients with primary immunodeficiencies associated with LRBA or CTLA-4 genetic mutation, what is the safety of abatacept compared with standard care?
3. In patients with primary immunodeficiencies associated with LRBA or CTLA-4 genetic mutation, what is the cost effectiveness of abatacept compared with standard care?
4. From the evidence selected, are there any subgroups of patients that may benefit from abatacept more than the wider population of interest?
5. From the evidence selected, what dose of abatacept was used?

See Appendix A for the full PICO document.

Review process

The methodology to undertake this review is specified by NHS England in its 'Guidance on conducting evidence reviews for Specialised Services Commissioning Products' (2020).

The searches for evidence were informed by the PICO document and were conducted on 8th August 2023.

See Appendix B for details of the search strategy.

Results from the literature searches were screened using their titles and abstracts for relevance against the criteria in the PICO document. Full text of potentially relevant studies were obtained and reviewed to determine whether they met the inclusion criteria for this evidence review.

See Appendix C for evidence selection details and Appendix D for the list of studies excluded from the review and the reasons for their exclusion.

Relevant details and outcomes were extracted from the included studies and were critically appraised using a checklist appropriate to the study design. See Appendices E and F for individual study and checklist details.

The available evidence was assessed by outcome for certainty using modified GRADE. See Appendix G for GRADE profiles.

4. Summary of included studies

Four studies were identified for inclusion (Catak et al 2022, Egg et al 2022, Kiykim et al 2019, Tesch et al 2020). Table 1 provides a summary of these included studies and full details are given in Appendix E.

Three studies reported retrospective case series and one (Kiykim et al 2019) reported a prospective case series.

No cost effectiveness studies were identified.

Table 1: Summary of included studies

Study	Population	Intervention and comparison	Outcomes reported
Catak et al 2022 Retrospective case series 16 centres in Turkey	29 patients (children and adults) with LRBA deficiency and 12 patients with CTLA-4 insufficiency Data for 23 patients with LRBA deficiency and 6 patients with CTLA-4 insufficiency treated with abatacept were extracted for inclusion in this review No subgroups reported	**Intervention** Abatacept maintenance dose 10-15 mg/kg per month LRBA deficiency group: median duration of treatment 30 months (range: 2.9-60) CTLA-4 insufficiency group: treatment duration not reported **Comparison** No comparator	**Critical outcome** • Symptom alleviation **Important Outcome** • Treatment failure

Egg et al 2022
 	
Retrospective case series
 	
Germany, Uruguay, Japan, Norway, Greece, Canada, Czech Republic, UK, Switzerland, Australia, USA, Spain, Korea, Denmark, Turkey, The Netherlands, Austria, Italy, Sweden
	123 patients (children and adults) with CTLA-4 mutation and symptoms related to CTLA-4 insufficiency requiring treatment
	
	29 patients were treated with abatacept; outcomes were reported for n=28 and these data were extracted for inclusion in this review
	
	Organ system involvement in those treated with abatacept:
	
	GLILD: n=10
	
	Gastrointestinal involvement: n=9
	
	Cytopenias: n=3
	
	Neurological involvement: n=6
		Intervention
		
		Abatacept 125 mg per week subcutaneously, sometimes with a loading dose of 500-1000 mg intravenously
		
		Treatment duration not reported
		
		Comparison
		
		No comparator
			Critical outcomes
			
			• Organ specific disease activity/ response:
			  ○ lung disease activity
			  ○ gastrointestinal disease activity
			  ○ haematological disease activity
			  ○ neurological disease activity
			
			Important Outcomes
			
			• None reported

Kiykim et al 2019
 	
Prospective case series
 	
12 centres in Turkey
	22 patients (children) with genetically-confirmed LRBA deficiency
	
	Data for 18 patients treated with abatacept and followed-up were extracted for inclusion in this review
		Intervention
		
		Abatacept 10 to 20 mg/kg/ every 1 to 4 weeks
		
		Median duration 12.5 months (range 5-33 months)
		
		Comparison
			Critical outcomes
			
			• Organ specific disease activity/ response:
			  ○ immune dysregulation symptoms (haematological and non-haematological)
			  ○ chronic diarrhoea
			  ○ lymphoproliferation

Study	Population	Intervention and comparison	Outcomes reported
	Clinical phenotype of patients treated with abatacept: Immune dysregulation: n=13 Chronic diarrhoea n=14 Lymphoproliferation n=10	No comparator	**Important Outcomes** • None reported
Tesch et al 2020 Retrospective case series 29 centres in Austria, Sweden, Israel, Belarus, Turkey, Spain, Belgium, Russia, Iran, Germany, Switzerland, UK, The Netherlands, Qatar, Italy, USA, Slovenia, Finland, Australia	76 patients (children and adults) with genetically confirmed LRBA deficiency based on presence of homozygous or compound heterozygous LRBA mutation Data for 23 patients treated with abatacept were extracted for inclusion in this review No subgroups reported	**Intervention** Abatacept (dose and treatment duration not reported) **Comparison** No comparator	**Critical outcomes** • Disease remission • Symptom alleviation **Important Outcomes** None reported **Safety**
Abbreviations CTLA-4: cytotoxic T lymphocyte antigen 4; LRBA: lipopolysaccharide-responsive beige-like anchor			

5. Results

In patients with primary immunodeficiencies associated with LRBA or CTLA-4 genetic mutation, what is the clinical effectiveness 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:** • One retrospective case series (Tesch et al 2020) (n=14) used a specially developed IDDA score[a] 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

[a] 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, complete remission of 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[b], 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 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,

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

Outcome	Evidence statement
	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. • 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.

6. Discussion

This evidence review considered the clinical effectiveness and safety of abatacept compared with standard care for the treatment of primary immunodeficiencies associated with LRBA or CTLA-4 genetic mutation. The critical outcomes of interest were disease remission, organ specific disease activity/response and symptom alleviation. Important outcomes were treatment failure, radiographic changes, quality of life, steroid use reduction and safety. Evidence on cost effectiveness was also sought.

No comparative studies were identified. Evidence was available from four case series including between 18 and 29 patients treated with abatacept. One prospective case series (Kiykim et al 2019) only included patients treated with abatacept. The other three studies (Catak et al 2022, Egg et al 2022 and Tesch et al 2020) were retrospective case series that aimed to describe clinical features of all patients meeting their eligibility criteria and used a range of treatments including abatacept. For these studies we only extracted information for patients treated with abatacept.

All four studies were judged to have a high risk of bias and certainty about the evidence for all critical and important outcomes was very low when assessed using modified GRADE.

There was heterogeneity between the studies in terms of their populations. One study included children and adults with LRBA deficiency or CTLA-4 insufficiency, one study included children and adults with CTLA-4 mutation and clinical symptoms, and two studies included patients with LRBA deficiency (one in children only, one in children and adults). None of the studies clearly reported clinical or demographic information of the participants, and none clearly indicated that they had consecutive or complete inclusion of participants. Two studies were conducted in Turkey, and two were multinational studies, both of which included sites in the UK. None of the studies reported demographic information of the included sites. The overall generalisability of the results to the UK NHS setting is unclear.

All four studies stated that they received funding from non-commercial grants.

Median duration of abatacept treatment was 12.5 months (range 5 to 33 months) in one study but duration of follow-up was not reported. A second study reported median treatment duration for some patients only of 30 months (range 2.9 to 60 months), and duration of follow-up for some patients only. One study reported 400 patient-months follow-up (range 0.1 to 5 years) for safety outcomes but did not report treatment duration. Both treatment duration and length of follow-up were not reported by one study. The dates of the studies ranged from 2005 to 2019. Details of additional treatment patients may have received were not clearly reported.

Outcomes were not well defined in any of the included studies. One study reported outcomes relating to disease remission, using a specially developed score to assess disease burden and treatment responses, but no details were provided on how the score was developed, its validity and reliability, or the clinical significance of the numerical scores reported. Two studies reported outcomes relating to organ-specific disease but neither used any organ-specific measures and outcomes were reported as ‘response’ or remission’ of the organ-specific disease activity, which was not defined. Two studies reported results relating to symptom alleviation, but this was not defined and no specific measures were used. There appeared to be some potential overlap between these outcomes due to the lack of definitions, for example the results judged to relate to symptom alleviation were limited to narrative information and could also be considered as relating to disease remission.

Catak et al 2022 reported that one patient had treatment stopped due to inadequate response after two years. We considered this to be related to treatment failure, although it was not

defined as such by the study. Two other studies reported that organ-specific disease did not respond to treatment in a number of patients; however it was not stated whether these patients had symptoms relating to other organs or systems, and if so whether or not these had responded to treatment, so it was not possible to say whether this represented overall treatment failure.

One study reported evidence on safety, but it was limited narrative information stating that certain events did not occur.

The certainty in the outcomes reported was very low in all studies. Factors reducing confidence in the outcomes reported include the retrospective design of three of the studies, the lack of comparators and small numbers of patients included, and the limited clinical and demographic information provided. It was unclear whether the recruitment of study participants was consecutive and complete. One study used a specially developed score with unclear validity, reliability and clinical significance; no other specific outcome measures were used in any of the studies and the outcomes reported were poorly defined.

No evidence was identified for the important outcomes of radiographic changes, quality of life or steroid use reduction. No evidence was identified on cost effectiveness.

There were no pre-specified subgroup analyses. Two studies reported remission of symptoms according to organ specific disease only, but 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 subgroup benefits more from abatacept treatment. No evidence was identified for subgroups of children and adults.

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, with the authors stating that abatacept doses could vary between centres. Egg et al 2022 used 125 mg per week subcutaneously, sometimes with a loading dose of 500-1000 mg intravenously.

7. Conclusion

This review included four case series that provide very low certainty evidence for the critical and important outcomes of disease remission, organ specific disease activity/response, symptom alleviation and treatment failure following treatment with abatacept for primary immunodeficiencies associated with LRBA or CTLA-4 genetic mutation, and one study provided very low certainty evidence on safety. No comparative studies were identified, so no conclusions can be reached about the clinical effectiveness or safety of abatacept compared with standard care. No evidence was identified for the important outcomes of radiographic changes, quality of life or steroid use reduction, and no evidence on cost effectiveness was found.

Outcomes were not well defined and information about duration of treatment, any other treatment received and duration of follow-up was lacking in some studies. However, the available very low certainty evidence suggests that symptom alleviation or full or partial disease remission occurs in most patients with primary immunodeficiencies associated with LRBA or CTLA-4 genetic mutation who were treated with abatacept, including patients with lung, gastrointestinal, haematological, lymphoproliferative, neurological and immune dysregulation. One retrospective case series provided very limited evidence about safety which suggested that non-severe adverse effects were experienced by very few patients treated with abatacept.

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. No evidence was identified comparing children and adults. The limitations of the studies and lack of comparative data limit the strength of the conclusions that can be drawn.

Appendix A PICO document

The review questions for this evidence review are:

1. In patients with primary immunodeficiencies associated with LRBA or CTLA-4 genetic mutation, what is the clinical effectiveness of abatacept compared with standard care?
2. In patients with primary immunodeficiencies associated with LRBA or CTLA-4 genetic mutation, what is the safety of abatacept compared with standard care?
3. In patients with primary immunodeficiencies associated with LRBA or CTLA-4 genetic mutation, what is the cost effectiveness of abatacept compared with standard care?
4. From the evidence selected, are there any subgroups of patients that may benefit from abatacept more than the wider population of interest?
5. From the evidence selected, what dose of abatacept was used?

P – Population and Indication	Patients with primary immunodeficiencies (PID) associated with LRBA or CTLA-4 genetic mutation. [Some other terms used to describe the population: • Granulomatous Lymphocytic Interstitial Lung Disease • Cytotoxic T-lymphocyte-associated protein 4 (CTLA4), CTLA4 deficiency, • T cell infiltration • Common variable immune deficiency (CVID) • Immune deficiency or Immunodeficiency • Human inborn errors of immunity (IEI) • Primary immune regulatory disorders (PIRD) • Primary immune deficiencies • Cytotoxic T lymphocyte antigen 4 (CTLA-4) haploinsufficiency (CHAI) • Lipopolysaccharide-responsive beige-like anchor (LRBA) deficiency with autoantibodies, regulatory T (Treg) cell defects, autoimmune infiltration, and enteropathy (LATAIE)] [CTLA-4 and LRBA mutations cause dysfunction of the regulatory T cell which results in autoimmune complications.] Subgroups of interest: • Organ specific disease e.g., lung, liver, skin, gut • Adults vs children
I – Intervention	Intravenous or subcutaneous abatacept given either as monotherapy or combination therapy. Abatacept may be given in combination with steroids +/- Immunoglobulin (Ig) replacement therapy.

	[Abatacept is a biological drug that specifically targets T_{Reg} cells.]
C – Comparators	Standard care which could include one or more of: • sirolimus • non-specific immune suppressant agents, such as azathioprine, mycophenolate mofetil • rituximab • allogenic hematopoietic stem cell transplantation (HSCT) • splenectomy These may all be given in combination with steroids +/- Ig replacement therapy.
O – Outcomes	**<u>Clinical Effectiveness</u>** Minimally clinically important differences (MCIDs) are not known unless stated. Outcomes reported at six to 12 months are of particular clinical interest. <u>*Critical to decision-making:*</u> • **Disease remission** *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.* • **Organ specific disease activity/ response** *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.* ○ ***Lung disease activity*** [Pulmonary function measures commonly used to assess this outcome are Forced Vital Capacity (FVC), Forced Expiratory Volume in 1 second (FEV1), the fraction between FVC and FEV1 (FVC/FEV1), diffusing capacity of the lungs for carbon monoxide (DLCO), peripheral oxygen saturation (SaO2). The 6 minutes walking test (6-MWT) can also be used. The Borg Rating of Perceived Exertion (RPE) is another commonly used measure. This is a measure of patient perceived breathlessness. An improvement of 1 point is considered a minimally clinically important difference.]

	○ ***Cutaneous disease activity*** [The Psoriasis Area and Severity Index (PASI) is a numeric score ranging from 0 to 72 and is often used to assess cutaneous disease activity. In general, a PASI score of 5 to 10 is considered moderate disease, and a score over 10 is considered severe.] ○ ***Hepatic (liver) disease activity*** [There are various liver disease scoring systems that can also be used including the Paediatric End-Stage Liver Disease (PELD) and Model for End-stage Liver Disease (MELD) scores.] ○ ***Gastrointestinal (Gut) disease activity*** [Gut disease activity is often measured by symptom scores such as The Gastrointestinal Symptom Rating Scale (GSRS), weight loss or gain and nutritional intake. The Inflammatory Bowel Disease Symptom Inventory (IBDSI) is a patient-report scale that provides an overview of how patients feel their symptoms are managed.] ○ ***Haematological disease activity*** [This is often measured by normalisation of blood counts and reduced frequency of haematological relapses.] • **Symptom alleviation** *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.* [Other terms used to describe or indicate symptom alleviation include but are not limited to symptoms, symptomatic response, alleviating disease symptoms. Symptom alleviation seen before six months may be significant to patients.] <u>*Important to decision-making:*</u> • **Treatment failure** *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. • **Radiographic changes** *Changes to the appearance of X-rays and scans of affected organs or systems are important to patients as they are used to help determine treatment success and requirement for further treatment. Given the irreversible features of lung fibrosis, imaging results might not be expected to return to normal, however, stabilisation may indicate treatment has successfully limited disease progression and may be associated with improvement in clinical features.* [X-rays, computerised tomography scans (CT), positron emission tomography (PET) and magnetic resonance imaging (MRI) can used to determine treatment changes.] • **Quality of life** *This is an important outcome for patients as it provides an indication of an individual's general health and self-perceived well-being and their ability to participate in activities of daily living. Validated tools for general quality of life measurements are important patient reported outcome measures to help inform patient-centred decision making and inform health policy. Disease specific quality of life measures are also useful for this purpose.* [Examples of quality-of-life tools include but are not limited to QLQ-OV28, QLQ-C30, EQ-5D and SF-36.] • **Steroid use reduction** *This outcome is important to those patients receiving steroids because steroid treatment is linked with iatrogenic health problems including osteoporosis, diabetes, hypertension, obesity, scarring and electrolyte disorders.* [A reduction of 5mg or more over a 6-month period would be considered a minimally clinically important difference.] **<u>Safety</u>** *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. [Infection control would be of particular interest in this patient group.] **Cost effectiveness**
Inclusion criteria	
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	All ages
Date limits	2013-2023
Exclusion criteria	
Publication type	Conference abstracts, non-systematic reviews, narrative reviews, commentaries, letters, editorials, guidelines and pre-prints.
Study design	Case reports, resource utilisation studies

Appendix B Search strategy

Medline, Embase, the Cochrane Library and TRIP database were searched limiting the search to papers published in English language in the last 10 years. Conference abstracts, commentaries, letters, editorials and case reports were excluded.

Search dates: 1 January 2013 to 8 August 2023

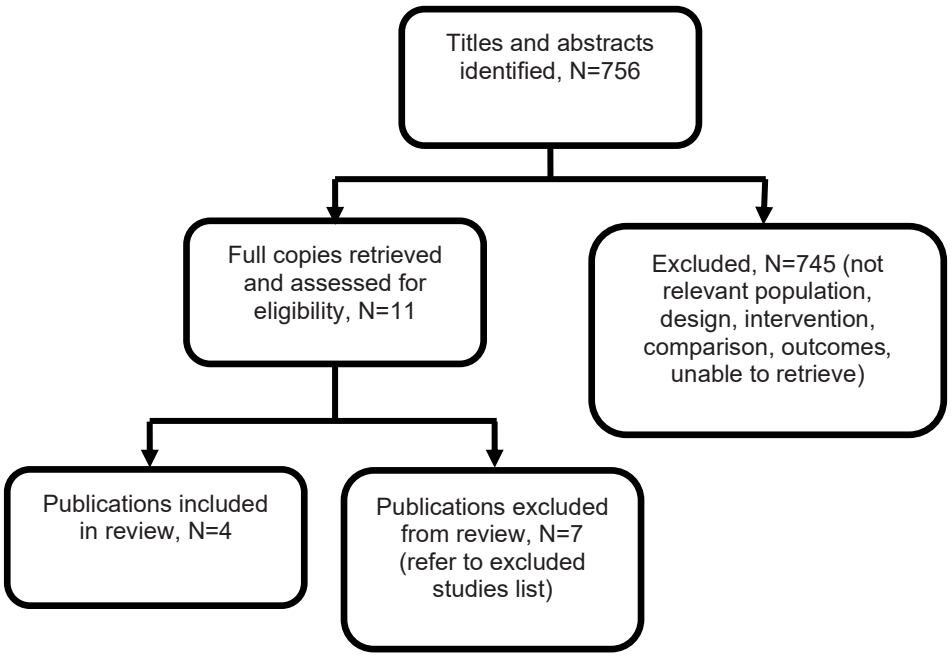
Medline search

- Abatacept/
- (abatacept or 21nglish).ti,ab,kf.
- 1 or 2
- immunologic deficiency syndromes/ or exp primary immunodeficiency diseases/
- (21nglis?deficiency or 21nglis* deficiency).ti,kf.
- (((primary or innate or inherited or common variable) adj (21nglis?deficienc* or 21nglis* deficienc* or immune regulatory disorder?)) or (pid or pird or cvid)).ab.
- ("human inborn errors of immunity" or iei).ti,ab,kf.
- ((combined or adenosine deaminase or common variable) adj (21nglis?deficienc* or 21nglis* deficienc*)).ti,ab,kf.
- recombinant activating gene*.ti,ab,kf.
- wiskott 21nglish syndrome?.ti,ab,kf.
- (hyper igm or hyper ige).ti,ab,kf.
- (((ligand or ctla4 or ctla-4 or cytotoxic t-lymphocyte* or xiap or x-linked inhibitor or iap3 or birca4 or antibod* or LRBA or "Lipopolysaccharide responsive beige like anchor") adj3 deficien*) or (chai or lataie)).ti,ab,kf.
- ((chronic granulomatous adj (disease? Or disorder?)) or (granulomatous adj3 (lung disease? Or pulmonary disease?))).ti,ab,kf.
- ((hemophagocytic or haemophagocytic) adj lymphohistiocytosis).ti,ab,kf.
- (phagocytic cell adj (disease or disorder?)).ti,ab,kf.
- 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15
- 3 and 16
- exp animals/ not humans/
- 17 not 18
- (commentary or letter or news or editorial).pt.
- 19 not 20
- limit 21 to (21nglish language and yr="2013 -Current")

Appendix C Evidence selection

The literature searches identified 756 references. These were screened using their titles and abstracts and 11 references were obtained in full text and assessed for relevance. Of these, four references are included in the evidence summary. The remaining seven references were excluded and are listed in Appendix D.

Figure 1- Study selection flow diagram



References submitted with Preliminary Policy Proposal

Reference	Paper selection – decision and rationale if excluded
Kiykim, A. et al. (2019) 'Abatacept as a long-term targeted therapy for LRBA deficiency', The Journal of Allergy and Clinical Immunology: In Practice, 7(8). Doi:10.1016/j.jaip.2019.06.011.	Included.
Rodina, Y. et al. (2021) 'Rituximab and abatacept are effective in differential treatment of interstitial lymphocytic lung disease in children with primary immunodeficiencies', Frontiers in Immunology, 12. Doi:10.3389/fimmu.2021.704261.	Excluded. Retrospective case series n=17 treated with abatacept but only 6 had LRBA or CTLA-4 deficiency and results not reported separately.
Lo, B. et al. (2015) 'Patients with LRBA deficiency show CTLA4 loss and immune dysregulation responsive to abatacept therapy', Science, 349(6246), pp. 436–440. Doi:10.1126/science.aaa1663.	Excluded. Case reports of n=6 treated with abatacept, no summary data reported. Case reports not eligible for inclusion, excluded due to study design.

Appendix D Excluded studies table

Study reference	Reason for exclusion
Lamers OAC, Smits BM, Leavis HL, de Bree GJ, Cunningham-Rundles C, Dalm VASH, et al. Treatment Strategies for GLILD in Common Variable Immunodeficiency: A Systematic Review. Frontiers in Immunology. 2021;12 (no pagination).	No combined data in SR. Individual studies assessed for relevance to PICO.
Yang L, Xue X, Chen X, Wu J, Yang X, Xu L, et al. Abatacept is effective in Chinese patients with LRBA and CTLA4 deficiency. Genes and Diseases. 2021;8(5):662-8.	Case reports n=3, no combined data. Larger case series available.
Bakhtiar S, Kaffenberger C, Salzmann-Manrique E, Donhauser S, Lueck L, Karaca NE, et al. Regulatory B cells in patients suffering from inborn errors of immunity with severe immune dysregulation. Journal of Autoimmunity. 2022;132 (no pagination).	Case series n=5. Larger case series available.
Rodina Y, Deripapa E, Shvets O, Mukhina A, Roppelt A, Yuhacheva D, et al. Rituximab and Abatacept Are Effective in Differential Treatment of Interstitial Lymphocytic Lung Disease in Children With Primary Immunodeficiencies. Frontiers in Immunology. 2021;12 (no pagination).	Retrospective case series n=17 treated with abatacept but only 6 had LRBA or CTLA-4 deficiency and results not reported separately.
Schwab C, Gabrysch A, Olbrich P, Patino V, Warnatz K, Wolff D, et al. Phenotype, penetrance, and treatment of 133 cytotoxic T-lymphocyte antigen 4-insufficient subjects. Journal of Allergy and Clinical Immunology. 2018;142(6):1932-46.	Exclude on intervention. Treatment with abatacept or belatacept n=14. Number with abatacept unclear.
Lo B, Zhang K, Lu W, Zheng L, Zhang Q, Kanellopoulou C, et al. Patients with LRBA deficiency show CTLA4 loss and immune dysregulation responsive to abatacept therapy. Science. 2015;349(6246):436-40.	Case reports of n=6 treated with abatacept, no summary data reported. Case reports not eligible for inclusion, excluded due to study design.
Von Spee-Mayer C, Echternach C, Agarwal P, Gutenberger S, Soetedjo V, Goldacker S, et al. Abatacept Use Is Associated with Steroid Dose Reduction and Improvement in Fatigue and CD4-Dysregulation in CVID Patients with Interstitial Lung Disease. Journal of Allergy and Clinical Immunology: In Practice. 2021;9(2):760-70.e10	Population do not meet the PICO as there is no evidence that they have the LRBA or CTLA-4 genetic mutation.

Appendix E Evidence table

For abbreviations see list after table

Study details	Population	Interventions	Study outcomes	Appraisal and funding
Catak MC, Akcam B, Bilgic Eltan S, Babayeva R, Karakus IS, Akgun G, et al. Comparing the levels of CTLA-4-dependent biological defects in patients with LRBA deficiency and CTLA-4 insufficiency. Allergy: European Journal of Allergy and Clinical Immunology. 2022;77(10):3108-23 **Study location** 16 centres in Turkey **Study type** Retrospective case series **Study aim** To compare clinical and laboratory features of LRBA deficiency and CTLA-4 insufficiency. **Study dates** Not reported.	**Inclusion criteria** Children and adults with a genetic diagnosis of LRBA deficiency or CTLA-4 insufficiency **Exclusion Criteria** Not reported. **Total sample size** LRBA deficiency: n=29 (n=23 treated with abatacept) CTLA-4 insufficiency n=12 (n=6 treated with abatacept) **Baseline characteristics** LRBA deficiency (n=23) Age at baseline: range 6 to 37 years Male: 52.2% Clinical diagnosis: CVID 52.2%, ALPS 21.7%, IPEX-like: 26.1% Median age of onset of abatacept therapy: 14.1 years (range 1.5-35 years)	**Interventions** Abatacept maintenance dose 10-15 mg/kg per month. LRBA deficiency (n=23): Median duration of treatment 30 months (range: 2.9-60) Not reported for patients with CTLA-4 insufficiency **Comparators** No comparator	**Critical outcomes** **Symptom alleviation** LRBA deficiency (n=23) Length of follow-up not stated. Authors state that all patients 'showed alleviation in symptoms' (but inadequate response in one patient after two years) CTLA-4 insufficiency (n=6) Length of follow-up: mean 6.8 years, SD 8.1 years). Authors state that 3 patients received abatacept and showed good responses at the maintenance dose. Outcomes not reported for the other 3 patients. **Important outcomes** **Treatment failure** LRBA deficiency (n=23) Abatacept was stopped due to inadequate response after two years in one patient. Not stated for patients with CTLA-4 insufficiency	This study was appraised using the JBI checklist for case series. 1. No 2. Yes 3. Unclear 4. Unclear 5. Unclear 6. Unclear 7. Unclear 8. No 9. No 10. Not applicable **Other comments:** Data were collected by questionnaire therefore the study appears to be retrospective, although this is not clearly stated. It is not stated whether patients or clinicians completed the questionnaire. Eligibility criteria are not reported and it is unclear how patients were selected or whether all eligible patients were included. Baseline demographics and clinical information were reported as individual patient data only. Only

Study details	Population	Interventions	Study outcomes	Appraisal and funding
	CTLA-4 insufficiency (n=6) Age at baseline: range 8 to 42 years Male: 50% Clinical diagnosis: CVID 66.7%. ALPS 33.3% Median age of onset not reported			limited narrative outcomes were reported. Duration of treatment was reported for patients with LRBA deficiency but not those with CTLA-4 insufficiency. Length of follow-up was not stated for patients with LRBA deficiency who were treated with abatacept, but was reported for three patients with CTLA-4 insufficiency. 'Symptom alleviation' and 'good response' were not defined. Results were not reported for 3 of the 6 patients with CTLA-4 insufficiency treated with abatacept. Adverse events were not reported. **Source of funding:** Grant from the Scientific and Technological Research Council of Turkey.
Egg D, Rump IC, Mitsuiki N, Rojas-Restrepo J, Maccari ME, Schwab C, et al. Therapeutic options for CTLA-4 insufficiency. Journal of Allergy and Clinical Immunology. 2022;149(2):736-46 **Study location** Centres (number not reported) in Germany, Uruguay, Japan, Norway, Greece, Canada, Czech Republic, UK, Switzerland, Australia, USA, Spain, Korea, Denmark, Turkey, The Netherlands, Austria, Italy, Sweden	**Inclusion criteria** Children and adults with CTLA-4 mutation and symptoms related to CTLA-4 insufficiency requiring treatment (clinically symptomatic). **Exclusion Criteria** Prespecified criteria not reported (excluded chromosome 2 deletion, missense variant p.N145S, missense variant p.T207A) **Total sample size** Total n=123 (n=29 treated with abatacept;	**Interventions** Abatacept 125 mg per week subcutaneously, sometimes with a loading dose of 500-1000 mg intravenously Duration of treatment not reported **Comparators** No comparator	**Critical outcomes** **Organ specific disease activity/ response** Length of follow-up not stated. *Lung disease activity* Patients with GLILD (n=10) Full response 5/10 Partial response 2/10 No response 1/10 No data 2/10 *Gastrointestinal disease activity*	This study was appraised using the JBI checklist for case series. 1. No 2. Unclear 3. Unclear 4. Unclear 5. Unclear 6. Unclear 7. No 8. No 9. No

Study details	Population	Interventions	Study outcomes	Appraisal and funding
Study type Retrospective case series **Study aim** To review clinical features, laboratory findings and response to treatment in an international cohort of CTLA-4 mutation carriers **Study dates** July 2014 to September 2017	outcomes were reported for n=28) **Baseline characteristics** Not reported for patients treated with abatacept. Organ system involvement in those treated with abatacept: GLILD: n=10 Gastrointestinal involvement: n=9 Cytopenias: n=3 Neurological involvement: n=6		Gastrointestinal involvement (n=9) Initial clinical response 9/9 Relapse of diarrhoea and abatacept discontinued 2/9 Response rate 7/9 (78%) *Haematological disease activity* Authors state abatacept was reported to be helpful in 1 patient with chronic ITP, in 1 patient with chronic AIHA, and in 1 patient with chronic PRCA *Neurologic involvement* Inflammatory central nervous system lesions (n=6) Response 4/6 (66.7%) No response 2/6	10. Not applicable **Other comments:** The study reports a retrospective review of patients from sites worldwide (number of sites not reported). Data were collected from participating physicians by questionnaire. Eligibility criteria are not clearly reported and it is unclear how patients were selected or whether all eligible patients are included. Participants were required to have symptoms related to CTLA-4 insufficiency requiring treatment, but the study does not describe how this was defined or measured. Treatment details were available for 117 of 123 eligible patients; it is possible that some of those with missing data received abatacept. Baseline demographics and clinical information were not reported for patients undergoing abatacept treatment. The study states 29 patients had abatacept but outcomes are reported for 28 patients. The abstract states the patients were followed until 2020 but this is not stated in the main text and duration of treatment was not reported. The study does not report how or when response was measured, other than it was based on clinician's judgment, or whether measurements were valid or reproducible. Adverse events were not reported. **Source of funding:**

Study details	Population	Interventions	Study outcomes	Appraisal and funding
				Funded by a number of non-commercial grants.
Kiykim A, Ogulur I, Dursun E, Charbonnier LM, Nain E, Cekic S, et al. Abatacept as a Long-Term Targeted Therapy for LRBA Deficiency. Journal of Allergy and Clinical Immunology: In Practice. 2019;7(8):2790-800.e15 **Study location** 12 centres in Turkey **Study type** Prospective case series **Study aim** To evaluate clinical and immunological responses to abatacept **Study dates** November 2016 to December 2018	**Inclusion criteria** Children with genetically confirmed LRBA deficiency. **Exclusion Criteria** Not reported. **Total sample size** n=22 (n=18 followed up) **Baseline characteristics** Not reported for n=18 with follow-up. All patients (n=22): Mean age at start of treatment 13.4 years (SD 7.9) Male: 14 (63.6%) Mean age of first symptoms 24 months (SD 23) Clinical phenotype of patients: Chronic diarrhoea n=14 Lymphoproliferation n=10 Immune dysregulation: n=13	**Interventions** Abatacept 10 to 20 mg/kg every 1 to 4 weeks Median duration 12.5 months (range 5-33 months) **Comparators** No comparator	**Critical outcomes** **Organ specific disease activity/ response** Length of follow-up not stated. Authors state that in all patients at least one of the symptoms was completely or partially controlled *Chronic diarrhoea* Complete remission 11/14 (78.6%) Partial remission 3/14 (21.4%) Non-responsive 0/14 *Lymphoproliferation* Complete remission 8/10 (80%) Partial remission 1/10 (10%) Non-responsive 1/10 (10%) *Immune dysregulation symptoms* Complete remission 5/13 (38.5%) Partial remission 4/13 (30.8%) Non-responsive 4/13 (30.8%) *Immune dysregulation symptoms: haematological immune dysregulation (AIHA, ITP) (n not stated)* Complete remission 80% Partial remission and non-responsive 20%	This study was appraised using the JBI checklist for case series. 1. No 2. Yes 3. Unclear 4. Unclear 5. Unclear 6. Unclear 7. Unclear 8. No 9. No 10. Not applicable **Other comments:** Prospective case series. Eligibility criteria are not clearly reported and it is unclear how patients were selected or whether all eligible patients are included. Twenty-two patients were recruited but only 18 were followed up (two not evaluated due to short-term duration of abatacept; reasons not stated for others). Baseline demographics and clinical information were reported as individual patient data only and not summarised for patients with follow-up. Abatacept regimens could vary between centres. Outcomes were not reported for two

Study details	Population	Interventions	Study outcomes	Appraisal and funding
			Immune dysregulation symptoms: other immune dysregulatory symptomatologies[c] *(n not stated)* Complete remission 10% Partial remission and non-responsive 90% Type 1 diabetes not reversible (n=3)	patients due to short-term duration of therapy. The study does not describe how or when remission was measured, or whether measurements were valid or reproducible. Adverse events were not reported. **Source of funding:** Grants from the Scientific and Technological Research Council of Turkey and National Institutes of Health
Tesch VK, Abolhassani H, Shadur B, Zobel J, Mareika Y, Sharapova S, et al. Long-term outcome of LRBA deficiency in 76 patients after various treatment modalities as evaluated by the immune deficiency and dysregulation activity (IDDA) score. Journal of Allergy and Clinical Immunology. 2020;145(5):1452-63 **Study location** 29 centres in Austria, Sweden, Israel, Belarus, Turkey, Spain, Belgium, Russia, Iran, Germany, Switzerland, UK, The Netherlands, Qatar, Italy,	**Inclusion criteria** Children and adults with genetically confirmed LRBA deficiency based on presence of homozygous or compound heterozygous LRBA mutation. **Exclusion Criteria** Not reported. **Total sample size** n=76 (23 treated with abatacept, 14 of these had abatacept monotherapy) **Baseline characteristics**	**Interventions** Abatacept (dose not reported) Duration of treatment not reported Other treatments in combination with abatacept (n=9) included sirolimus, nivaquine, mycophenolate mofetil and adalimumab **Comparators** No comparator	**Critical outcomes** **Disease remission** Follow-up for all 23 patients was 400 patient-months (range 0.1 to 5 years). Duration of treatment and length of follow-up was not reported for the 14 patients with abatacept monotherapy. n=14 treated with abatacept monotherapy *IDDA score* [d] Median IDDA score (range) Before treatment: 34 (9 to 57) After treatment: 18.5 (4.8 to 45.2) Before versus after, p=0.0039 **Symptom alleviation**	This study was appraised using the JBI checklist for case series. 1. No 2. Yes 3. Unclear 4. Unclear 5. Unclear 6. Unclear 7. Unclear 8. No 9. No 10. Unclear

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

[d] 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.

Study details	Population	Interventions	Study outcomes	Appraisal and funding
USA, Slovenia, Finland, Australia **Study type** Retrospective case series **Study aim** To describe the clinical course of patients with LRBA deficiency who do and do not receive a transplant. **Study dates** 2005 to 2019	Age at last visit: range 3 to 55 years Male: 52%		n=14 treated with abatacept monotherapy 10 patients (71.4%) were reported to show a good general response with an amelioration of almost all symptoms. 3 patients (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. In 1 patient (7.1%) only autoimmune cytopenia could be resolved, but lymphoproliferation, parenchymal lung disease, endocrinopathy, failure to thrive, and severe infections were refractory to abatacept. **Safety (n=23)** Follow-up 400 patient-months (range 0.1 to 5 years). 0/23 had immunosuppression-associated malignancy. 0/23 had an increase in susceptibility to infections. 2/23 had newly developed eczema 21/23 had no reported side effects	**Other comments:** Retrospective case series with patients from 29 sites worldwide, but there is no information about the location of the patients treated with abatacept. Eligibility criteria are not clearly reported and it is unclear whether all eligible patients were included. Data were obtained by retrospective chart review. Baseline demographics and clinical information are reported as individual patient data only. The study included a total of 76 patients; the clinical outcomes reported in this review are those for the 14 patients who received abatacept monotherapy. Safety outcomes are reported for the 23 patients who received either abatacept monotherapy or abatacept along with one or more other treatments. The authors also refer to the patients with abatacept monotherapy as 'under no or different immunosuppressive treatment after the initiation of abatacept only'; it is unclear what this means. Duration of treatment and length of follow-up were not reported for the 14 patients with abatacept monotherapy. Outcomes were based on a specially developed score which was stated by the authors to assess disease burden and treatment response, but the validity and reliability of this is not reported. There is no indication of the clinical significance of scores and while there was reported to be a statistically significant decrease in the median score in the group of patients

Study details	Population	Interventions	Study outcomes	Appraisal and funding
				treated with abatacept only, it is not possible to assess the clinical significance of this. Other outcomes are not clearly reported and are not reported for all patients treated with abatacept. Limited data on adverse events are reported. **Source of funding:** Funded by a number of non-commercial grants.

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; IPEX: immunodysregulation, polyendocrinopathy, enteropathy, X-linked; ITP: immune thrombocytopenia; LRBA: lipopolysaccharide-responsive beige-like anchor; PRCA: pure red cell aplasia; SD: standard deviation

Appendix F Quality appraisal checklists

JBI Critical Appraisal Checklist for Case Series

1. Were there clear criteria for inclusion in the case series?
2. Was the condition measured in a standard, reliable way for all participants included in the case series
3. Were valid methods used for the identification of the condition for all participants included in the case series?
4. Did the case series have consecutive inclusion of participants?
5. Did the case series have complete inclusion of participants?
6. Was there clear reporting of the demographics of the participants in the study?
7. Was there clear reporting of clinical information of the participants?
8. Were the outcomes or follow up results of cases clearly reported?
9. Was there clear reporting of the presenting site(s)/clinic(s) demographic information?
10. Was statistical analysis appropriate?

Appendix G GRADE profiles

Table 2: 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?

For footnotes and abbreviations see end of table

Outcome measure, units and timepoint in study (for continuous outcomes indicate if benefit is indicated by higher or lower result)									
QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Abatacept	No comparator	Result		
Disease remission (1 retrospective case series)									
IDDA score[a] at unspecified length of follow-up (benefit is indicated by lower result)									
1 retrospective case series Tesch et al 2020	Very serious limitations[1]	Very serious indirectness[2]	Not applicable	Not calculable	14		Median IDDA score (range) (n=14) Before treatment: 34 (9 to 57) After treatment: 18.5 (4.8 to 45.2) Before versus after, p=0.0039	Critical	Very low
Organ specific disease activity / response (1 retrospective case series, 1 prospective case series)									
Response (based on physician's judgement) in lung disease activity in patients with GLILD at unspecified length of follow-up									
1 retrospective case series Egg et al 2022	Very serious limitations[3]	Very serious indirectness[2]	Not applicable	Not calculable	10		Full response 5/10 (50%) Partial response 2/10 (20%) No response 1/10 (10%) No data 2/10 (20%)	Critical	Very low
Response (based on physician's judgement) in gastrointestinal activity in patients with gastrointestinal involvement at unspecified length of follow-up									
1 retrospective case series Egg et al 2022	Very serious limitations[3]	Very serious indirectness[2]	Not applicable	Not calculable	9		Response rate 7/9 (78%) Initial clinical response followed by relapse 2/9 (22%)	Critical	Very low
Remission (not defined) of chronic diarrhoea at unspecified length of follow-up									
1 prospective case series Kiykim et al 2019	Very serious limitations[3]	Very serious indirectness[2]	Not applicable	Not calculable	14		Complete remission 11/14 (78.6%) Partial remission 3/14 (21.4%)	Critical	Very low
Response (based on physician's judgement) in inflammatory nervous system lesions in patients with neurological involvement at unspecified length of follow-up									
1 retrospective case series Egg et al 2022	Very serious limitations[3]	Very serious indirectness[2]	Not applicable	Not calculable	6		Response 4/6 (66.7%) No response 2/6 (33.3%)	Critical	Very low

Outcome measure, units and timepoint in study (for continuous outcomes indicate if benefit is indicated by higher or lower result)									
QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Abatacept	No comparator	Result		
Response (based on physician's judgement) in haematological disease activity at unspecified length of follow-up									
1 retrospective case series Egg et al 2022	Very serious limitations[3]	Very serious indirectness[2]	Not applicable	Not calculable	3		Abatacept reported to be 'helpful' in 3/3 (100%) (1 with chronic ITP, 1 with chronic AIHA, 1 with chronic PRCA)	Critical	Very low
Remission (not defined) of lymphoproliferation at unspecified length of follow-up									
1 prospective case series Kiykim et al 2019	Very serious limitations[3]	Very serious indirectness[2]	Not applicable	Not calculable	10		Complete remission 8/10 (80%) Partial remission 1/10 (10%) Non-responsive 1/10 (10%)	Critical	Very low
Remission (not defined) of immune dysregulation symptoms at unspecified length of follow-up									
1 prospective case series Kiykim et al 2019	Very serious limitations[3]	Very serious indirectness[2]	Not applicable	Not calculable	13		Complete remission 5/13 (38.5%) Partial remission 4/13 (30.8%) Non-responsive 4/13 (30.8%)	Critical	Very low
Remission (not defined) of immune dysregulation symptoms: haematological immune dysregulation (AIHA, ITP) at unspecified length of follow-up									
1 prospective case series Kiykim et al 2019	Very serious limitations[3]	Very serious indirectness[2]	Not applicable	Not calculable	Not reported		Complete remission 80% Partial remission and non-responsive 20%	Critical	Very low
Remission (not defined) of immune dysregulation symptoms: other immune dysregulatory symptomatologies[b] at unspecified length of follow-up									
1 prospective case series Kiykim et al 2019	Very serious limitations[3]	Very serious indirectness[2]	Not applicable	Not calculable	Not reported		Complete remission 10% Partial remission and non-responsive 90% Type 1 diabetes not reversible (n=3)	Critical	Very low
Control or partial control of at least one symptom at unspecified length of follow-up									
1 prospective case series Kiykim et al 2019	Very serious limitations[3]	Very serious indirectness[2]	Not applicable	Not calculable	18		18/18 (100%): At least one of the symptoms was reported to be completely or partially controlled	Critical	Very low
Symptom alleviation (2 retrospective case series)									

Outcome measure, units and timepoint in study (for continuous outcomes indicate if benefit is indicated by higher or lower result)									
QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Abatacept	No comparator	Result		
Narrative report of symptom alleviation at unspecified length of follow-up									
1 retrospective case series Catak et al 2022	Very serious limitations[3]	Very serious indirectness[2]	Not applicable	Not calculable	29		LRBA deficiency (n=23) 23/23 (100%) reported to show 'alleviation in symptoms' (but 'inadequate response' in one patient after two years) CTLA-4 insufficiency (n=6); 3/6 (50%) reported to show good responses 3/6 (50%) outcomes were not reported	Important	Very low
Narrative report of symptom alleviation at unspecified length of follow-up									
1 retrospective case series Tesch et al 2020	Very serious limitations[1]	Very serious indirectness[2]	Not applicable	Not calculable	14		10/14 (71.4%) reported to show a good general response with amelioration of almost all symptoms. 3/14 (21.4%) reported to show neither a decrease in disease activity in different organ systems nor an amelioration of signs of autoimmunity and immune dysregulation. 1/14 (7.1%) reported to have resolution of autoimmune cytopenia only (lymphoproliferation, parenchymal lung disease, endocrinopathy, failure to thrive, and severe infections were refractory to abatacept).	Important	Very low
Treatment failure (1 retrospective case series)									
Number of patients with treatment stopped due to inadequate response after two years									
1 retrospective case series Catak et al 2022	Very serious limitations[3]	Very serious indirectness[2]	Not applicable	Not calculable	23		1/23 (4.3%)	Important	Very low

Outcome measure, units and timepoint in study (for continuous outcomes indicate if benefit is indicated by higher or lower result)									
QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Abatacept	No comparator	Result		
Safety (1 retrospective case series)									
Safety during 400 patient-months follow-up (range 0.1 to 5 years)									
1 retrospective case series Tesch et al 2020	Very serious limitations[1]	Very serious indirectness[2]	Not applicable	Not calculable	23		0/23 immunosuppression-associated malignancy. 0/23 increase in susceptibility to infections. 2/23 (8.7%) newly developed eczema after abatacept initiation 21/23 (91%) no reported side effects	Important	Very low

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

1 Risk of bias: very serious limitations due to absence of clear eligibility criteria, incomplete inclusion of participants, unclear reporting of demographics and clinical information, unclear reporting of outcomes, and appropriateness of statistical analysis unclear.
2 Indirectness: very serious indirectness due to no comparison across treatment arms, limited information about study population and unclear alignment of outcomes with PICO.
3 Risk of bias: very serious limitations due to absence of clear eligibility criteria, incomplete inclusion of participants, unclear reporting of demographics and clinical information, unclear reporting of outcomes, and lack of any statistical analysis or summary statistic.

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.
b Diabetes, alopecia, arthritis, demyelinating disease, granulomatous-lymphocytic interstitial lung disease.

Glossary

Adverse event	Any undesirable event experienced by a person while they are having a drug or any other treatment or intervention, regardless of whether or not the event is suspected to be related to or caused by the drug, treatment or intervention.
Baseline	The set of measurements at the beginning of a study (after any initial 'run-in' period with no intervention), with which subsequent results are compared.
Bias	Systematic (as opposed to random) deviation of the results of a study from the 'true' results, which is caused by the way the study is designed or conducted.
Case series	Reports of several patients with a given condition, usually covering the course of the condition and the response to treatment. There is no comparison (control) group of patients.
Clinical importance	A benefit from treatment that relates to an important outcome such as length of life and is large enough to be important to patients and health professionals.
Comparator	The standard (for example, another intervention or usual care) against which an intervention is compared in a study. The comparator can be no intervention (for example, best supportive care).
Cost effectiveness study	An analysis that assesses the cost of achieving a benefit by different means. The benefits are expressed in non-monetary terms related to health, such as life years gained (that is, the number of years by which life is extended as a result of the intervention). Options are often compared on the cost incurred to achieve 1 outcome (for example, cost life year gained).
GRADE (Grading of recommendations assessment, development and evaluation)	A systematic and explicit approach to grading the quality of evidence and the strength of recommendations developed by the GRADE working group.
Minimal clinically important difference	The smallest change in a treatment outcome that people with the condition would identify as important (either beneficial or harmful), and that would lead a person or their clinician to consider a change in treatment.
PICO (population, intervention, comparison and outcome) framework	A structured approach for developing review questions that divides each question into 4 components: the population (the population being studied); the interventions (what is being done); the comparators (other main treatment options); and the outcomes (measures of how effective the interventions have been).
Prospective study	A research study in which the health or other characteristic of patients is monitored (or 'followed up') for a period of time, with events recorded as they happen. This contrasts with retrospective studies.
P-value (p)	The p value is a statistical measure that indicates whether or not an effect is statistically significant. For example, if a study comparing 2 treatments found that 1 seems to be more effective than the other, the p value is the probability of obtaining these results by chance. By convention, if the p value is below 0.05 (that is, there is less than a 5% probability that the results occurred by chance), it is considered that there probably is a real difference between treatments. If the p value is 0.001 or less (less than a 0.1% probability that the results occurred by chance), the result is seen as highly significant. If the p value shows that there is likely to be a difference between treatments, the confidence interval describes how big the difference in effect might be.

Retrospective study	A research study that focuses on the past and present. The study examines past exposure to suspected risk factors for the disease or condition. Unlike prospective studies, it does not cover events that occur after the study group is selected.
Statistical significance	A statistically significant result is one that is assessed as being due to a true effect rather than random chance.

References

Included studies

- Catak MC, Akcam B, Bilgic Eltan S, Babayeva R, Karakus IS, Akgun G, et al. Comparing the levels of CTLA-4-dependent biological defects in patients with LRBA deficiency and CTLA-4 insufficiency. Allergy: European Journal of Allergy and Clinical Immunology. 2022;77(10):3108-23.
- Egg D, Rump IC, Mitsuiki N, Rojas-Restrepo J, Maccari ME, Schwab C, et al. Therapeutic options for CTLA-4 insufficiency. Journal of Allergy and Clinical Immunology. 2022;149(2):736-46.
- Kiykim A, Ogulur I, Dursun E, Charbonnier LM, Nain E, Cekic S, et al. Abatacept as a Long-Term Targeted Therapy for LRBA Deficiency. Journal of Allergy and Clinical Immunology: In Practice. 2019;7(8):2790-800.e15.
- Tesch VK, Abolhassani H, Shadur B, Zobel J, Mareika Y, Sharapova S, et al. Long-term outcome of LRBA deficiency in 76 patients after various treatment modalities as evaluated by the immune deficiency and dysregulation activity (IDDA) score. Journal of Allergy and Clinical Immunology. 2020;145(5):1452-63.

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