Public Health Evidence Report Following Engagement Activity

This form is to be completed by the Policy Working Groups Public Health Lead if stakeholders identify potential new evidence during policy development engagement activities. The Public Health Lead will assess the evidence raised to against the Population, Intervention, Comparator and Outcome (PICO) criteria and will record the studies in the appropriate boxes in the '*Outcome for studies suggested during engagement activities*' section of this form. In cases where newly identified evidence has a material impact please return the completed form to the Clinical Effectiveness Team (CET).

URN	**2309**
Policy title:	**Abatacept for autoimmune complications of primary immunodeficiencies caused by CTLA-4 or LRBA genetic mutation**
CRG:	**Immunology & Allergy**
NPOC:	**Blood & Infection**
Engagement activity	
Date	**11/03/2024**

Description of comments during engagement (If studies have been suggested please provide a list of references)	Missing evidence: The publication: Therapeutic modalities and clinical outcomes in a large cohort with LRBA deficiency and CTLA4 insufficiency. Taghizade, N et al. J Allergy Clin Immunol. 2023 Dec;152(6):1634-1645. doi: 10.1016/j.jaci.2023.08.004. Epub 2023 Aug 16.PMID: 37595759

Action taken by Public Health lead	Reviewed the full text of the submitted paper against the existing Evidence Review and PICO to understand if it was new evidence and what if anything it contributed additionally to the evidence base, and whether it materially alters the conclusions of the existing evidence review.
Outcome for studies suggested during engagement activities	
1. Evidence already identified during the evidence review	N/a
2.New evidence identified by stakeholders that does not fall within PICO and search methodology	N/a
3.New evidence identified by stakeholders that falls within PICO and search methodology but does not materially affect the conclusions of the existing evidence review	N/a

4.New evidence identified by stakeholders that falls within PICO and search methodology, that does materially affect the conclusions of the existing evidence review. Updated evidence review to be undertaken (to be agreed with CET)	Taghizade, N et al. J Allergy Clin Immunol. 2023 Dec;152(6):1634-1645. doi: 10.1016/j.jaci.2023.08.004. Epub 2023 Aug 16.PMID: 37595759 The Tagnizade et al study was excluded from the evidence review because its publication date (16/08/23) August 2023) fell eight days after the literature search was conducted (08/08/23). Otherwise, it does meet all the PICO criteria: - Population: Patients with confirmed LRBA and CTLA4 mutations. - Intervention: Abatacept - Control: Hematopoietic stem cell transplantation (HSCT), and immunosuppressants other than abatacept - Outcome: o Clinical effectiveness: including symptom alleviation (critical outcome); Radiographic changes (important outcome) – pre/post analysis only; treatment failure (important outcome. o Safety: Frequency of side effects including serious incidents. o Subgroups: Results disaggregated by LBRA and CLTA4 patients showing differences in disease progression and response to treatment between sub-groups. The study is a prospective (non-randomised) comparator cohort study. The study population comprised 98 patients with confirmed LRBA and CTLA4 mutations. The patients were recruited from 24 different immunology centres in Turkey. Patients were enrolled in the study at different time points starting in November 2016 and followed up prospectively until February 2023. The patients were followed and evaluated at baseline and every 6 months for clinical manifestations and response to the respective therapies, namely immunosuppressants, abatacept, and HSCT treatments. The median duration of abatacept therapy was 2.3 years (min-max = 0.8-6.7 years), with a maintenance intravenous dose of 10 to 20 mg/kg per 3 to 4 weeks in 53 patients (91.3%) and a subcutaneous dose of 125 mg/per week in 5 patients (8.7%). <u>Key findings</u>: The LRBA–/– patients exhibited a more severe disease course than did the CTLA41/– patients, requiring more immunosuppressants, abatacept, and HSCT to control their symptoms. The probability of OS was better in CTLA41/– patients than in LRBA–/– patients (91.6% vs 60.5%, respectively [P = .008])

	Among the 58 patients who received abatacept as either a primary or rescue therapy, sustained complete control was achieved in 46 (79.3%) without severe side effects. The rate of abatacept use was higher in LRBA–/– patients than in CTLA41/– patients (n = 42 [66.7%] vs n = 16 [42.6%]; P = .02) In contrast, most patients who received immunosuppressants as primary therapy (n = 61) showed either partial or no disease control (72.1%), necessitating additional immunosuppressants, abatacept, or transplantation. The difference in efficacy of therapeutic approaches between abatacept and other immunosuppressants was evaluated by using PSM propensity Score Matching). Patients who received only abatacept (n = 25) as the treatment group and patients who used only immunosuppressants (n = 20) as the control group were compared. The outcome was the difference in CR rate between the groups. After the PSM matching analysis, the study found that 18 patients in the treatment group matched with 18 members of the control group with standardized mean differences less than 0.2 for the analysed covariates. Receiving only abatacept versus the other immunosuppressants showed a statistically better CR rate (72.2% vs 33.3% [P = .04; OR = 5.2; 95% CI = 1.25-12.57]) In patients who received abatacept either as a primary or rescue therapy abatacept demonstrated an increased control of disease manifestations, demonstrating a CR in 74% of LRBA–/– patients and 93% of CTLA41/– patients compared with other Immunosuppressants (CR in 22% of LRBA–/– patients and 54% of CTLA41/–) Figure 4 below shows the greater disease control and side effect profile of abatacept and immunosuppressants.

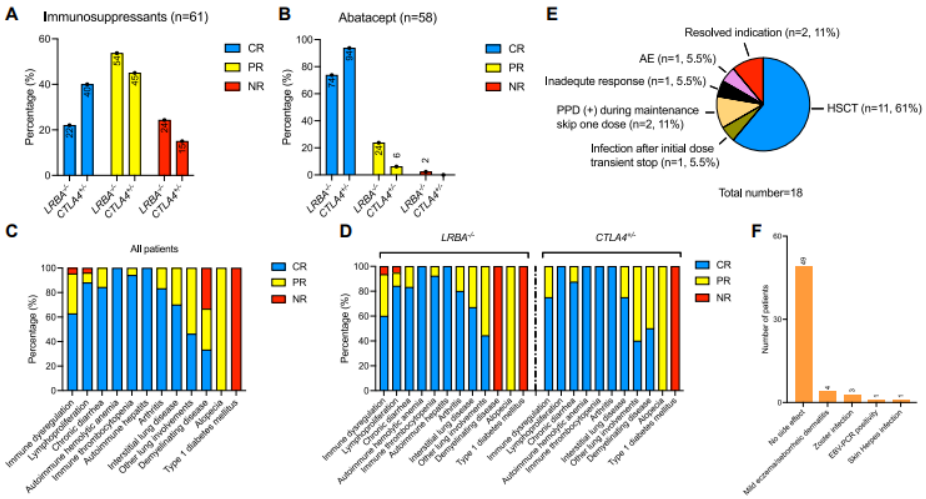

FIG 4. Abatacept demonstrates better disease control with fewer side effects than with other immunosuppressants. Levels of symptom control after immunosuppressants (**A**) or abatacept (**B**). Impact of abatacept on various disease symptoms in all patients (**C**) and in *LRBA*$^{-/-}$ patients and *CTLA4*$^{+/-}$ patients (**D**). **E,** Reasons for abatacept discontinuation during the study. **F,** Number of patients experiencing side effects during abatacept use. *AE,* Adverse effect; *PPD,* Purified Protein Derivative.

Patients with partial or no response to abatacept (n = 12) had longer disease activity before abatacept therapy, with higher organ involvement and poorer disease outcomes than those with a complete response.

HSCT was performed in 14 LRBA–/– patients; 9 patients (64.2%) showed complete remission, and 3 (21.3%) continued to receive immunosuppressants after transplantation.

HSCT and abatacept therapy gave rise to similar probabilities of survival.

Figure 7 (below) demonstrates that abatacept provides survival similar to that achieved by undergoing transplantation, whereas probability of survival with other IS's is lower than transplant.

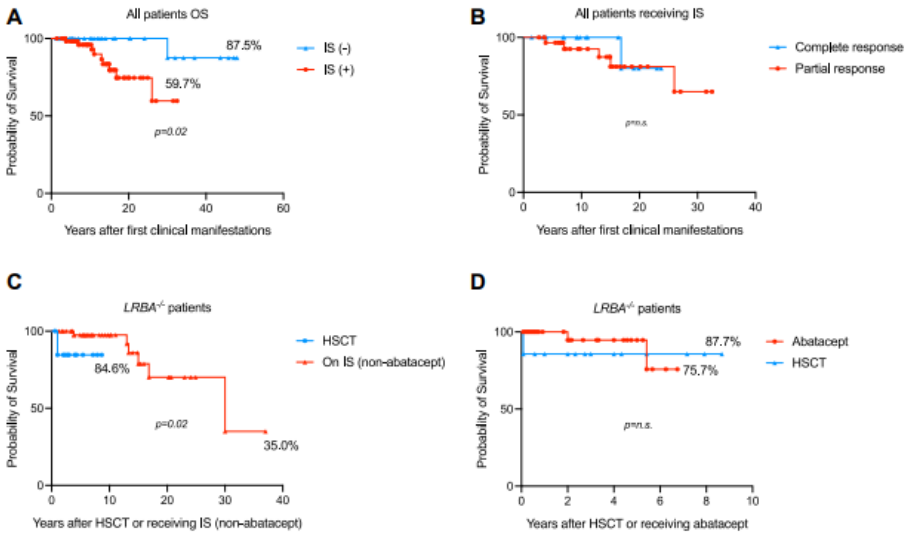

FIG 7. Receiving abatacept provides survival similar to that with achieved by undergoing transplantation. **A,** Impact of receiving immunosuppressants (ISs) on survival. **B,** Comparison of survival between patients who show CRs and PRs to ISs. Probability of survival with HSCT versus with ISs (**C**) or abatacept (**D**).

The conclusion of the paper is that Abatacept is superior to immunosuppressants in controlling disease manifestations over the long term, especially when started early, and it may provide a safe and effective therapeutic alternative to transplantation.

The study considerably strengthens the findings of the review for several reasons:

- Size. Although the study includes some of the same patients included within Catak et al study within the evidence review *(Catak MC, et al 2022)* this is a much larger study (98 patients, 58 treated with Abatacept) than any of the four studies identified, which include between 18 and 29 patients treated with abatacept.

- Design: Unlike the four studies included in the evidence review (three of which were retrospective case series and one which was a prospective case series), the Taghizade, et al study is a prospective (non-randomized) comparative study.

- Outcomes included: The Taghizade et al study provides evidence against several critical and important outcomes of interest that are not covered by the evidence review. Specifically in relation to side effects, subgroup analysis and some clinical outcomes including before/after radio-graphic changes.

The current evidence reviews conclusion states that *"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…" For these reasons it is likely that the Taghizade et al study would strengthen the grade of the findings, and potentially increase the prioritisation of the resulting policy.

Completed by:	Public Health Consultant
Date:	15/04/2024

Peer reviewed and supported by:	(add name and role or add N/A in both boxes if point 4 above is N/A)
Date:	