Wu *et al. Cardiovascular Diabetology* (2025) 24:146
https://doi.org/10.1186/s12933-025-02696-7

Cardiovascular Diabetology

REVIEW Open Access

Anti-CD3 monoclonal antibody in treating patients with type 1 diabetes: an updated systematic review and meta-analysis

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Abstract

Objective To evaluate the efficacy of anti-CD3 monoclonal antibody (mAb) in patients with type 1 diabetes (T1D) and identify the influencing factors.

Methods Randomized controlled trials comparing anti-CD3 mAb with placebo or standard care in T1D participants were screened from PubMed, Embase, and Cochrane databases until 31 May 2024. Changes in area under the curve (AUC) of C-peptide, HbA1c level and daily insulin requirement were main outcomes. Results were computed as standardized mean difference (SMD) and 95% confidence interval (CI). Meta-regression and subgroup analyses were also performed.

Results Eleven eligible trials involving 1573 T1D participants were included in this meta-analysis. Compared with control group, anti-CD3 mAb significantly increased AUC of C-peptide (SMD = 0.337, 95% CI 0.105 to 0.569, $P = 0.004$) and decreased daily insulin requirement (SMD = −0.598, 95% CI −0.927 to −0.269, $P < 0.001$). Subgroup analysis revealed that low average age (≤ 18 years old: SMD = 0.546, 95% CI 0.203 to 0.889, $P < 0.001$), high cumulative dose of anti-CD3 mAb (≥ 25 mg: SMD = 0.588, 95% CI 0.424 to 0.752, $P < 0.001$), and short T1D diagnosis duration before enrollment (≤ 6 weeks: SMD = 0.609, 95% CI 0.405 to 0.814, $P < 0.001$) were significantly associated with an increase in AUC of C-peptide. Notably, meta-regression analysis revealed that cumulative dose was the most critical factor, masking the effect of average age and T1D diagnosis duration. Most adverse events were transient and could be medically treated.

Conclusion Anti-CD3 mAb effectively preserves C-peptide secretion and reduces insulin requirement in patients with T1D. Younger age (≤ 18 years), earlier treatment initiation (≤ 6 weeks post-diagnosis), higher cumulative doses (≥ 25 mg) may present better therapeutic effect.

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Research insights

What is currently known about this topic? Humanized anti-CD3 mAb could preserve pancreatic β-cell function in patients with T1D.

What is the key research question? What kinds of patients with T1D would benefit more from anti-CD3 mAb treatment?

What is new? Young age (≤ 18 years), early treatment (≤ 6 weeks after diagnosis) and enough cumulative doses (≥ 25 mg) of anti-CD3 mAb would enable patients with T1D to achieve a better preservation of pancreatic β-cell function. Cumulative dose is the most critical factor that affects the efficacy of anti-CD3 mAb treatment.

How might this study influence clinical practice? Our findings appeal to early treatment with enough doses of anti-CD3 mAb for people with T1D.

Keywords Anti-CD3 monoclonal antibody, C-peptide, Immunotherapy, Type 1 diabetes

Background

Type 1 diabetes (T1D) is an autoimmune disease in which pancreatic β-cells are destroyed by T lymphocytes [1], leading to the irrecoverable decline in β-cell mass and function followed by the absolute deficiency of insulin secretion. The incidence and prevalence of T1D are increasing globally. An estimated 8.4 million individuals were diagnosed with T1D in 2021, and this number is projected to climb to 13.5–17.4 million by 2024 (60–107% higher than that in 2021) [2].

The therapy of T1D relies on insulin replacement, supplying exogenous insulin to satisfy blood glucose control. However, the long-term insulin treatment could not restore β-cell mass, and β-cell function still decreases with the disease progression [3]. The autoimmunity plays important roles in the pathogenesis of T1D [4]. Therefore, therapies targeting autoimmunity, including cyclosporine, anti-inflammatory drugs, T cell-targeted therapy, B cell-targeted therapy and antigen-based therapies, were developed [4, 5]. The animal studies and clinical trials demonstrated that the immunotherapy strategy, especially anti-CD3 monoclonal antibody (mAb) treatment, has the ability to protect β-cell function, suggestive of the huge potential for T1D therapy [5–7].

Anti-CD3 mAb has been initially applied in the prevention of allograft rejection after transplant and has outweighed other novel immune therapies in autoimmunity [8]. Targeting both pathogenic and regulatory T cells, anti-CD3 mAb acts on ongoing diseases and restores self-tolerance without exacerbating autoimmune diseases due to its transient immunosuppression [8]. Animal studies revealed that treatment with anti-CD3 mAb in non-obese diabetic mice could reverse the disease. After treatment with a 5-mg daily dose of anti-CD3 mAb (145-2C11) for 5 consecutive days, complete and permanent remission of diabetes was observed within 2 or 4 weeks [6, 7]. Randomized controlled trials (RCTs) have also provided insight into the impressive effect of humanized anti-CD3 mAb (teplizumab or otelixizumab) on the preservation of C-peptide response (an important indicator of β-cell function) in patients with T1D [9–12]. Recently, the Food and Drug Administration (FDA) has approved teplizumab as a medication for delaying T1D progression to stage 3 (clinical) T1D among individuals who are 8 years or older and have stage 2 T1D (defined by two or more diabetes-related autoantibodies and elevated blood glucose but no diabetic symptoms) [13]. However, most of the anti-CD3 mAb therapies could not significantly reduce the level of glycated hemoglobin (HbA1c), an important parameter for glycemic control reflecting the average blood glucose levels for 3 months [14]. The reduction of HbA1c could assist in mitigating the decrease of C-peptide responses in patients with T1D as well [15]. Besides, the included patients had different characteristics (e.g., age, disease course, and baseline C-peptide response) and received different treatment regimens (including drug category, cumulative dose, and treatment duration) in the reported studies [10, 12, 16–19], which might result in different conclusions.

To clarify the efficacy of anti-CD3 mAb in protecting T1D individuals against the disease progression, several systematic reviews and meta-analyses were conducted. However, those analyses either concentrated on the single anti-CD3 mAb teplizumab [20, 21] or failed to detect heterogeneity source [22]. Herein, we aimed to perform an updated systematic review and meta-analysis of all the available RCTs of anti-CD3 mAb treatment versus placebo or standard care in patients with T1D, including a recently published RCT with a considerable sample size [16] to assess the outcomes of efficacy and safety. Notably, we also did the fine-grained subgroup analysis (stratified by age, treatment initiation time and cumulative dose) to investigate which factor affects the efficacy of the anti-CD3 mAbs and causes the heterogeneity. Therefore, this updated meta-analysis may be more helpful for the future clinical applications of anti-CD3 mAb treatment.

Methods

This systematic review and meta-analysis, registered at the International Prospective Register of Systematic Reviews (registration no. CRD42024547146), was performed according to Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines.

Data sources and searches

The systematic literature search was conducted from PubMed, Embase and the Cochrane Library with keywords of "type 1 diabetes mellitus", "anti-CD3 monoclonal antibody" and "randomized controlled trial" for trials written in English. The initial time for searching was not limited and it was stopped on 31 May 2024. No restriction for follow-up duration and sample size. Detailed search strategies can be found in Additional file 1: Tables S1, S2 and S3.

Eligibility criteria and study selection

We included the studies met the following criteria: (1) T1D participants; (2) anti-CD3 mAb treatment; (3) RCTs; (4) interested endpoints were reported: area under the curve (AUC) of C-peptide, HbA1c level, daily insulin requirement and adverse events (AEs). Exclusion criteria were as follows: (1) reviews, case reports, meeting reports, observational studies, or animal studies; (2) reporting only pharmacokinetic parameters; (3) missing essential data necessary for analysis; (4) a combination of teplizumab or otelixizumab with any of other interventions.

Selection processes were as follows: (1) search results from databases were downloaded into EndNote 20.0.0.16480 (Clarivate Analytics) and duplicates were removed; (2) abstracts and titles were screened by two reviewers (QW and RW) independently and removed irrelevant articles; (3) the remained full-text articles were assessed and the ineligible articles were removed; (4) all the included studies were re-evaluated by two viewers (XL and XC). Any disagreement between the two reviewers was solved by the third reviewer (HW or TH).

Data extraction

The two viewers independently extracted the following relevant data from all the included articles: (1) interested parameters: changes in AUC of C-peptide, HbA1c level and daily insulin requirement; (2) study information: the first author, published year, study design, sample size, T1D diagnosis duration before enrollment, intervention regimen, cumulative dose of treatment, and follow-up duration; (3) baseline characteristics of participants, including age, AUC of C-peptide, HbA1c level, and daily insulin requirement; (4) reported AEs. We converted the data using a standard formula or the GetData Graph Digitizer (version 2.26) if the mean or standard deviation (SD) was not provided. To estimate the cumulative dose of anti-CD3 mAb, 50 kg or 1.75 m^2 was exploited as the body weight or surface area (if possible) in the trials in which average age was between 12 and 18 years old. Arranging the cumulative doses in ascending order, we observed that 25 mg could facilitate an even partition of two subgroups, and was therefore regarded as the cut-off value for the subgroup analysis. All the data were double-checked.

Risk of bias and publication bias assessment

Using the Cochrane Collaboration's tool for assessing the risk of bias in randomized trials [23], the risks of the included trials were assessed from four domains: (1) random sequence generation; (2) allocation concealment; (3) blinding; and (4) incomplete outcome data. Funnel plots, *Begg* test and *Egger's* test were performed to assess publication bias.

Statistical analysis

The means and SDs of the changes in AUC of C-peptide, HbA1c level and daily insulin requirement between baseline and post-intervention were employed to estimate the pooled effect. The results were computed as the standardized mean difference (SMD) and 95% confidence interval (CI). The meta-analysis and meta-regression analysis were performed using the *meta* package (version 7.0–0) in R software (version 4.3.3). The heterogeneity of the included trials was assessed using the I^2 statistics, and heterogeneity should be considered when $I^2 > 50\%$. The fixed effect model was utilized to synthesize the study effects when $I^2 < 50\%$, otherwise a random effect model was exploited. Subgroup analysis was employed to explore the effect of anti-CD3 mAb according to the results of meta-regression analysis with $P < 0.05$. Sensitivity analysis was performed to determine the source of heterogeneity. Results were deemed statistically significant if $P < 0.05$.

Results

Search results

The articles (N = 194) from the three databases PubMed (N = 57), Embase (N = 54) and Cochrane Library (N = 83) were downloaded into EndNote software. Duplicated records (N = 69) were excluded and 125 studies were further screened. Eighty-eight records were excluded by title and abstract according to the criteria. Full-text assessment excluded 26 articles for ineligible study design (N = 15), participants (N = 2) and outcomes (N = 4), or without available outcomes (N = 1), or with other therapies (N = 2), or belonging to the same trial with a shorter follow-up duration (N = 2) as shown in Fig. 1. Eleven eligible RCTs were finally included in this systematic review and meta-analysis.

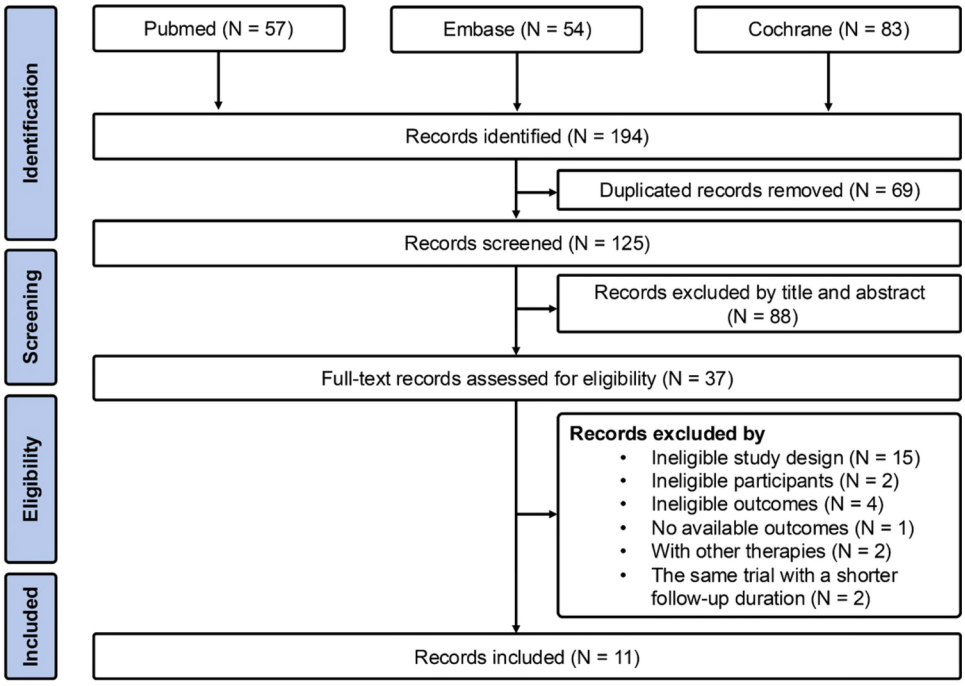

Fig. 1 PRISMA flowchart

Study characteristics

Characteristics of 11 RCT studies [9, 10, 12, 16, 17, 19, 24–28] involving 1573 T1D individuals (1093 in intervention group and 480 in control group) were summarized (Additional file 1: Table S4). Four studies were open-labeled, while the rest used a placebo control. The age of T1D participants ranged from 7.5 to 45 years old. Participants enrolled in the RCTs were within 6 weeks after T1D diagnosis in seven studies, less than 3 months in five studies, and between 4 weeks and 12 months in one study. Otelixizumab was supplied in four studies, while Teplizumab was applied in the rest. The detailed intervention regimen and the computed cumulative doses were shown in Additional file 1: Table S4. The cumulative doses were divided into the two groups, <25 mg and ≥ 25 mg. The follow-up duration was categorized as 1 year and >1 year. Baseline characteristics of participants in the included trials were shown in Additional file 1: Table S5.

Quality of included studies

The risks of bias summary and graph were shown in Additional file 2: Fig. S1 and S2. Only the trial of Herold 2009 [26] was regarded as high-risk study, and the overall risk of bias was completely low. The funnel plot showed a symmetric pattern, suggesting a low risk of publication bias of the included studies (Additional file 2: Fig. S3), which was further confirmed by the *Begg* test ($P=0.767$) and *Egger's* test ($P=0.212$; Additional file 1: Table S6).

Efficacy of anti-CD3 mAb intervention

Change in AUC of C-peptide

Eleven trials involving 1346 T1D participants who had the data of AUC of C-peptide were pooled in this meta-analysis (Fig. 2). Overall, T1D individuals receiving anti-CD3 mAb intervention had a higher AUC of C-peptide (SMD = 0.337, 95% CI 0.105 to 0.569, $P=0.004$; substantial heterogeneity, $I^2=68.4\%$, $P<0.001$) than those in control group.

Change in HbA1c level

One trial did not report the endpoints of HbA1c level and daily insulin requirement. Thus, 10 trials involving 1415 participants who had the HbA1c data were pooled in this meta-analysis (Fig. 3A). There was no significant difference between the intervention and control groups (SMD = −0.071, 95% CI −0.348 to −0.206, $P=0.615$; substantial heterogeneity, $I^2=71.2\%$, $P<0.001$) in terms of change in HbA1c level.

Change in daily insulin requirement

The data of change in daily insulin requirement in 10 trials involving 1183 individuals were pooled in this meta-analysis (Fig. 3B). Compared with the control group, anti-CD3 mAb intervention remarkably reduced daily insulin requirement in T1D individuals (SMD = −0.598, 95% CI −0.927 to −0.269, $P<0.001$; substantial heterogeneity, $I^2=88.5\%$, $P<0.001$).

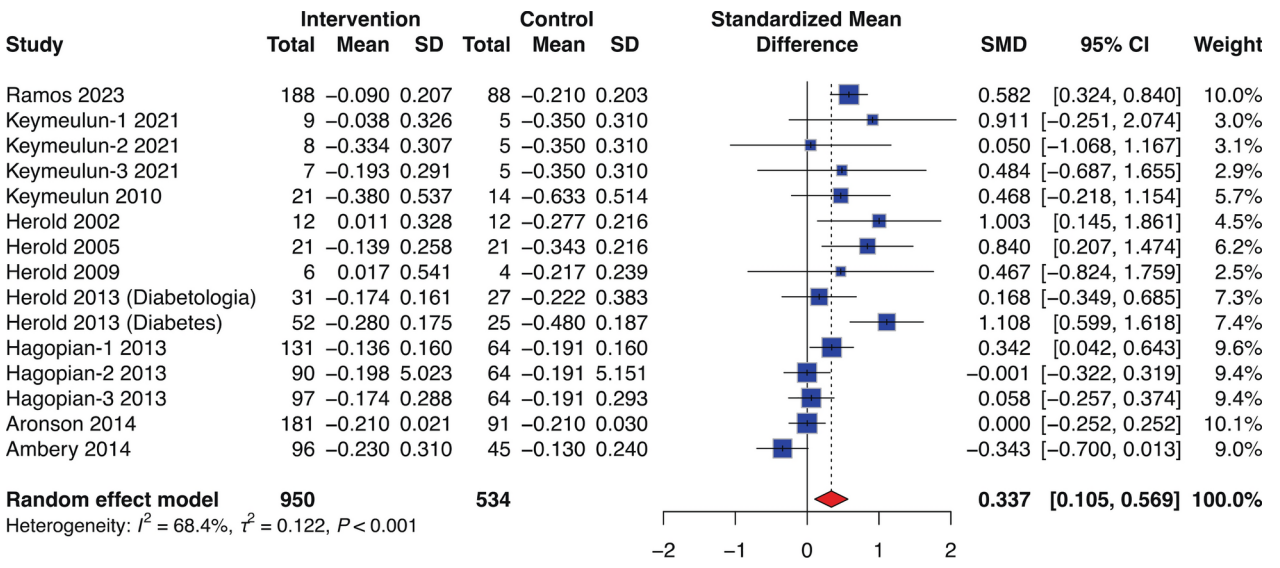

Fig. 2 Forest plot for meta-analysis of change in AUC of C-peptide. Keymeulun-1 2021, Keymeulun-2 2021 and Keymeulun-3 2021 from the same trial represented the different anti-CD3 mAb doses of 9 mg, 18 mg and 27 mg, respectively. Hagopian-1 2013, Hagopian-2 2013 and Hagopian-3 2013 from the same trial represented the different anti-CD3 mAb doses of 9034 μg/m^2, 2985 μg/m^2 and 2426 μg/m^2, respectively. If I^2 < 50%, a fixed effect model was utilized, otherwise a random effect model. AUC, area under the curve; CI, confidence interval; SD, standard deviation; SMD, standardized mean difference

Meta-regression and subgroup analyses

Meta-regression analysis was conducted with average age and AUC of C-peptide at baseline, as well as T1D diagnosis duration before enrollment ≤ 6 weeks (yes or no), category of anti-CD3 mAb (otelixizumab or teplizumab), cumulative dose of treatment (< 25 mg or ≥ 25 mg) and follow-up duration (1 year or > 1 year) as the covariates.

Change in AUC of C-peptide

Meta-regression analysis showed that baseline average age (β = − 0.046, 95% CI − 0.085 to − 0.007, P = 0.022), cumulative dose (≥ 25 mg: β = 0.619, 95% CI 0.363 to 0.874, P < 0.001), and T1D diagnosis duration before enrollment (≤ 6 weeks: β = 0.471, 95% CI 0.057 to 0.885, P = 0.026) were significantly associated with the change in AUC of C-peptide, while baseline AUC of C-peptide, drug categories and follow-up duration did not show such an association (Table 1). The average age, cumulative dose, and T1D diagnosis duration could partly explain the heterogeneity that occurred in the meta-analysis model, with 47.3%, 91.7%, and 38.9% heterogeneity, respectively. Further meta-regression analysis by combining two factors revealed that the effect of baseline average age (model 1: β = − 0.023, 95% CI − 0.052 to 0.006, P = 0.113) and T1D diagnosis duration (model 2: β = 0.133, 95% CI − 0.229 to 0.496, P = 0.470) on change in AUC of C-peptide was masked by the cumulative dose of anti-CD3 mAb (Table 2). Moreover, the combination of two factors illustrated much higher heterogeneity than the single one (95.3% *vs.* 47.3% and 89.4% *vs.* 38.9% for average age and T1D diagnosis duration, respectively).

Subgroup analysis for average age, cumulative dose and T1D diagnosis duration showed that individuals who was ≤ 18 years old (SMD = 0.546, 95% CI 0.203 to 0.889, P < 0.001; Fig. 4A), receiving cumulative doses ≥ 25 mg (SMD = 0.588, 95% CI 0.424 to 0.752, P < 0.001; Fig. 4B), and starting treatment within 6 weeks after T1D diagnosis (SMD = 0.609, 95% CI 0.405 to 0.814, P < 0.001; Fig. 4C) had a larger increase in AUC of C-peptide, while their counterpart subgroups (i.e., > 18 years old, < 25 mg, and > 6 weeks) showed insignificant effects. The significant differences existed between the two cumulative dose subgroups (P < 0.001, Fig. 4B), and low heterogeneity was detected within the subgroups (< 25 mg: I^2 = 6.6%; ≥ 25 mg: I^2 = 15.2%; Fig. 4B), which meant that the cumulative dose was the critical parameter leading to the overall substantial heterogeneity (I^2 = 68.4%, Fig. 2), thereby causing the different efficacies in C-peptide secretion preservation. The change in AUC of C-peptide was statistically different between the two average age subgroups (P = 0.038, Fig. 4A) and between the two T1D diagnosis duration subgroups (P = 0.012, Fig. 4C). The low heterogeneities were found within the subgroups of average age > 18 years old group (I^2 = 43.5%, Fig. 4A) and T1D diagnosis duration ≤ 6 weeks (I^2 = 0%, Fig. 4C), but substantial heterogeneity remained to be evident within the subgroups of average age ≤ 18 years old and T1D diagnosis duration > 6 weeks (Fig. 4A and C). These results suggested that average age and treatment initiation time were the influencing variables but could not totally explain the heterogeneity sources of change in AUC of C-peptide.

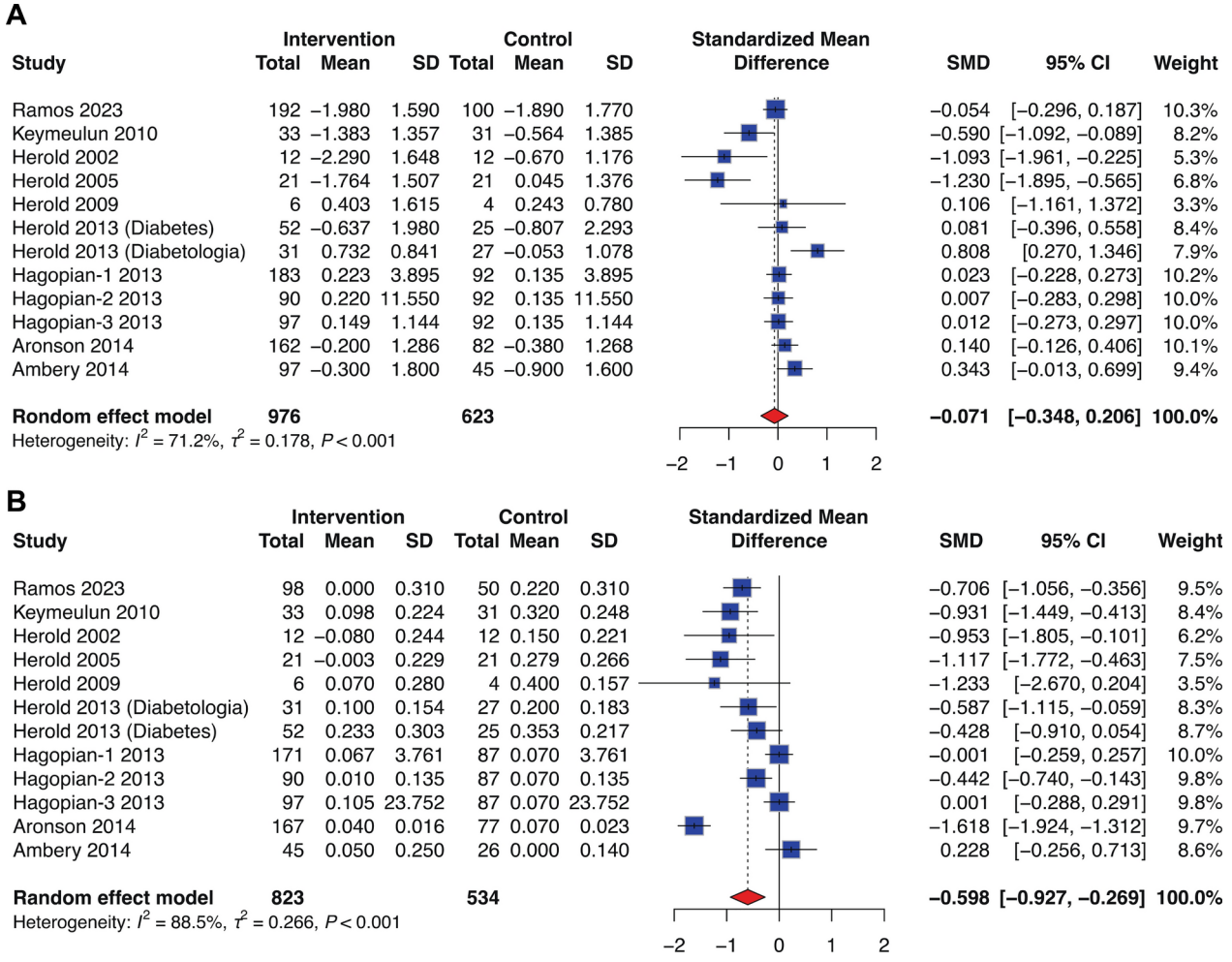

Fig. 3 Forest plot for meta-analysis of change in HbA1c level (**A**) and daily insulin requirement (**B**). Hagopian-1 2013, Hagopian-2 2013 and Hagopian-3 2013 from the same trial represented the different anti-CD3 mAb doses of 9034 μg/m^2, 2985 μg/m^2 and 2426 μg/m^2, respectively. If I^2 < 50%, a fixed effect model was utilized, otherwise a random effect model was employed. CI, confidence interval; SD, standard deviation; SMD, standardized mean difference

Table 1 Meta-regression of change in AUC of C-peptide (single factor)

Variables	β (95% CI)	P	R^2
Average age	− 0.046 (− 0.085, − 0.007)	0.022	47.3
Baseline AUC of C-peptide	− 1.251 (− 3.560, 1.058)	0.288	4.97
Cumulative dose			91.7
< 25 mg	Reference	–	
≥ 25 mg	0.619 (0.363, 0.874)	< 0.001	
Drug category			19.8
Otelixizumab	Reference	–	
Teplizumab	0.346 (− 0.111, 0.802)	0.138	
Follow–up duration			21.0
1 year	Reference	–	
> 1 years	0.345 (− 0.109, 0.799)	0.136	
T1D diagnosis duration ≤ 6 weeks			38.9
No	Reference	–	
Yes	0.471 (0.057, 0.885)	0.026	

AUC Area under the curve, *CI* Confidence interval, *T1D* Type 1 diabetes.

Table 2 Meta-regression of change in AUC of C-peptide (two factors)

Variables	β (95% CI)	P	R^2
Model 1: cumulative dose combined with age			95.4
Dose ≥ 25 mg	0.499 (0.221, 0.777)	< 0.001	
Average age	− 0.023 (− 0.052, 0.006)	0.113	
Model 2: cumulative dose combined with T1D diagnosis duration			89.4
Dose ≥ 25 mg	0.548 (0.217, 0.879)	0.001	
T1D diagnosis duration ≤ 6 weeks, yes	0.133 (− 0.229, 0.496)	0.470	

AUC Area under the curve, *CI* Confidence interval, *T1D* Type 1 diabetes.

Change in HbA1c level

Meta-regression analysis showed that cumulative dose (≥ 25 mg: β = − 0.551, 95% CI − 1.014 to − 0.087, P = 0.020) and T1D diagnosis duration before enrollment

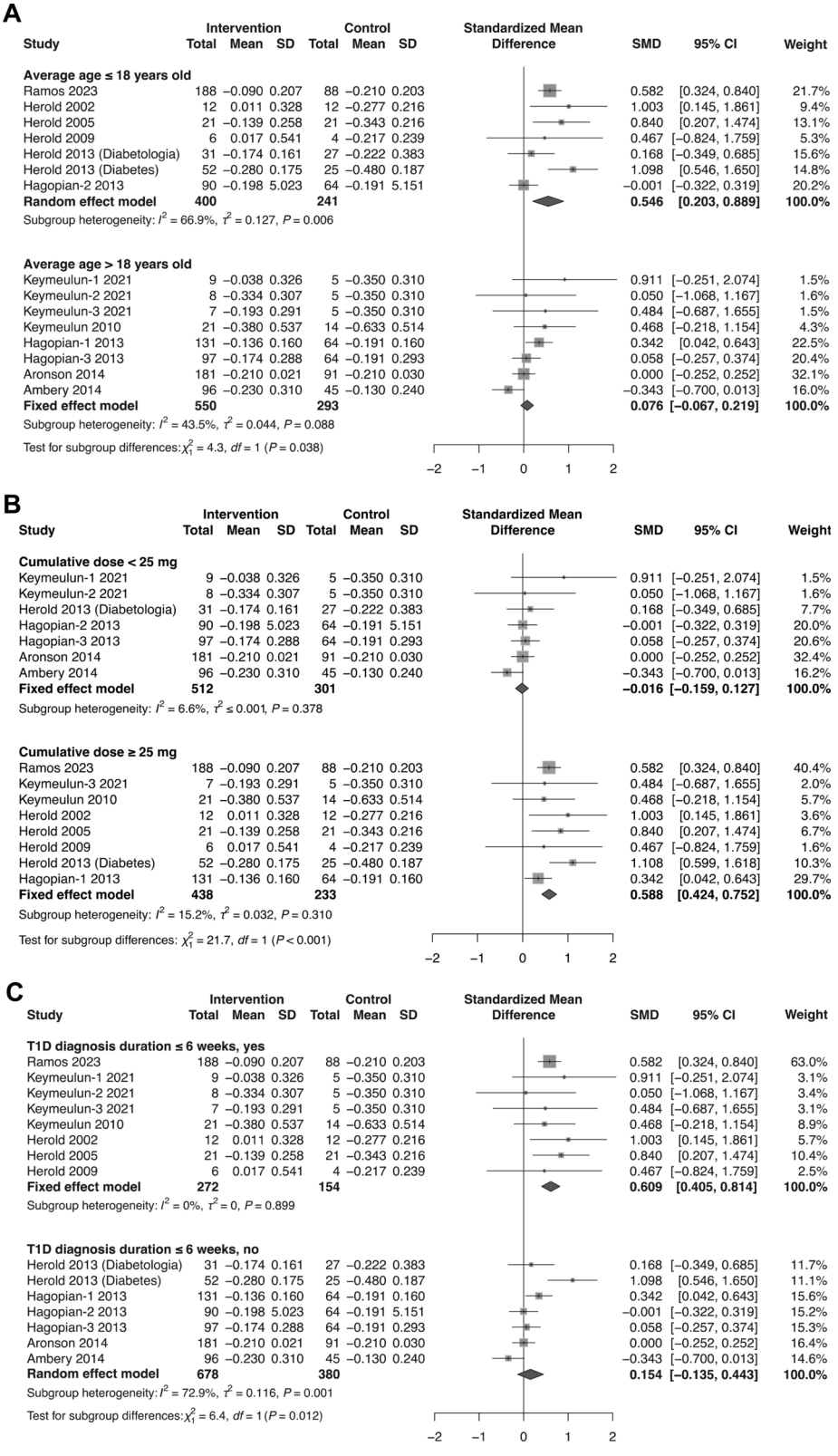

Fig. 4 Forest plot for meta-analysis of change in AUC of C-peptide in subgroups stratified by average age (**A)** cumulative dose of anti-CD3 mAb (**B)** and T1D diagnosis duration (**C)**. Keymeulun-1 2021, Keymeulun-2 2021 and Keymeulun-3 2021 from the same trial represented the different anti-CD3 mAb doses of 9 mg, 18 mg and 27 mg, respectively. Hagopian-1 2013, Hagopian-2 2013 and Hagopian-3 2013 from the same trial represented different anti-CD3 mAb doses of 9034 μg/m^2, 2985 μg/m^2 and 2426 μg/m^2, respectively. If I^2 < 50%, a fixed effect model was utilized, otherwise a random effect model was employed. AUC, area under the curve; CI, confidence interval; SD, standard deviation; SMD, standardized mean difference; T1D, type 1 diabetes

(≤6 weeks: $\beta = -0.682$, 95% CI −1.112 to −0.252, $P = 0.002$) were variables influencing the change in HbA1c level, while average age, baseline AUC of peptide, drug category, and follow-up duration were not (Additional file 1: Table S7). Subgroup analysis revealed that HbA1c level was significantly reduced only in the subgroup of T1D diagnosis duration ≤6 weeks (SMD = −0.573, 95% CI −1.082 to −0.063, $P < 0.001$; Additional file 2: Fig. S4B). Both cumulative dose and T1D diagnosis duration exhibited subgroup differences ($P = 0.017$ and $P = 0.009$, Additional file 2: Fig. S4), but non-negligible heterogeneities were observed in the two cumulative dose subgroups and in the subgroup of T1D diagnosis duration ≤6 weeks, suggesting that these two stratifications might slightly cause the differences in the efficacy of anti-CD3 mAb in lowering HbA1c level but were not the primary reasons.

Change in daily insulin requirement

None of the covariates was significantly associated with change in daily insulin requirement in meta-regression analysis (Additional file 1: Table S8). Hence, subgroup analysis was not carried out in this endpoint and the source of heterogeneity could not be identified as well.

Sensitivity analysis

Sensitivity analysis was conducted to observe whether removing any single trial could affect the results and heterogeneity for the change in AUC of C-peptide. No significant alteration in the results and heterogeneity was observed (Additional file 2: Fig. S5), even omitting the trial with high-risk bias (Herold 2009) [26].

Adverse events

Among the included trials, AEs were reported in different ways. Overall or specified categories of AEs were reported in seven studies [12, 16, 17, 24, 25, 27, 28], while AEs according to the grade stratification 1–5 or serious AEs were reported in five trials [12, 16, 17, 27, 28]. Two studies reported AEs in the control group [9, 26], and one trial did not report AEs [10]. The most common AEs appeared in both intervention and control groups were headache, nausea, fatigue, lymphopenia and fever. The rash and mild cytokine release syndrome were seen more frequently in anti-CD3 mAb-treated individuals [17]. Some trials reported higher rate of AEs or severe AEs in the anti-CD3 mAb group versus placebo or standard care [12, 27], while the other trials did not reveal such an effect although the rate of treatment discontinuation due to AEs was higher than placebo [16, 17]. One study found that the frequency and severity of AEs were dose-dependent [12]. Nonetheless, no evidence of long-term toxic effects was documented [22], and the AEs were mostly mild to moderate, transient and manageable [12, 16, 17, 28].

Discussion

This updated systematic review and meta-analysis pooled 11 trials involving 1573 T1D participants, who were treated with anti-CD3 mAb (otelixizumab or teplizumab, n = 1093) or with placebo or standard care (n = 480), to evaluate the efficacy of anti-CD3 mAb in increasing AUC of C-peptide, and reducing HbA1c level and daily insulin requirement. The main findings are as follows: (1) anti-CD3 mAb was efficacious in the preservation of C-peptide secretion and reduction of daily insulin requirement, albeit did not have a significant effect on HbA1c level in T1D individuals; (2) meta-regression and subgroup analyses indicated that higher cumulative dose (≥25 mg), lower baseline average age (<18 years), and shorter treatment initiation time (≤6 weeks after T1D diagnosis) might benefit more in C-peptide secretion preservation; (3) cumulative dose explained the heterogeneity source of change in AUC of C-peptide, and was the most dominant factor covering the effects of average age and treatment initiation time; (4) cumulative dose (≥25 mg) and early treatment of anti-CD3 mAb (≤6 weeks) might also have potential advantages in reducing HbA1c level. Unfortunately, we failed to identify the heterogeneity origin of change in HbA1c level and daily insulin requirement.

Previous RCTs found that immunotherapies for T1D had the potential for preserving C-peptide secretion and reducing daily insulin requirement [5, 16–18], suggestive of β-cell protection. However, those RCTs displayed the different characteristics of participants and different treatment regimens, which might result in the different efficacies. Therefore, several systematic reviews and meta-analyses were conducted, and found that anti-CD3 mAb functioned in preserving C-peptide secretion and decreasing daily insulin requirement in T1D individuals [20–22, 29, 30]. Besides, Liu et al. showed that higher cumulative doses (≥17 mg) were associated with a better C-peptide response improvement. However, they did not report the heterogeneity source, a critical variable that caused the discrepancies among studies [22]. In our meta-analysis, we found that higher cumulative dose (≥25 mg) not only significantly preserved the C-peptide secretion, but also was the essential influencing factor that explained 91.7% heterogeneity. With low heterogeneity within both ≥25 mg and <25 mg subgroups, cumulative dose may be the heterogeneity origin that result in the different efficacies of anti-CD3 mAb. The reasons for the inconsistent findings between our meta-analysis and others might be due to the different sample sizes (T1D individuals were updated in our meta-analysis, especially with 296 new-onset T1D individuals in the study of Romas et al. [16]), the distinct ways for estimating the cumulative dose, the different cumulative dose cut-off value, and the varied data extract methods from the original articles. Notably, our two-factor meta-regression

analysis showed that cumulative dose covered the effect of average age and treatment initiation time on the preservation of C-peptide secretion. However, the importance of these influencing variables was not evaluated in most of previous meta-analyses [20–22, 29].

We showed that younger T1D individuals (≤ 18 years old) was associated with a better efficacy of anti-CD3 mAb. Consistently, Liu et al. also found that baseline age (≤ 18 years old) was associated with the therapeutic effect of anti-CD3 mAb [22]. By contrast, Grando Alves et al. failed to detect a significant difference between the age subgroups (8–11 years versus 12–17 years) [21]. This difference may be because T1D children and adolescents (≤ 18 years old) might equally benefit from anti-CD3 mAb treatment. The influence of age on the efficacy of anti-CD3 mAb might be explained by the age-dependency of the insulitis process as it diminishes with increasing age. Keymeulen et al. reported that the loss of residual β-cell function in the placebo subgroup was more rapid and pronounced in younger individuals than in older ones [19]. Thus, the intervention of anti-CD3 mAb might benefit more for adolescents by delaying the deterioration of residual β-cell function.

In our subgroup analysis, early anti-CD3 mAb treatment (within 6 weeks after T1D diagnosis) improved C-peptide secretion and might reduce HbA1c level, while the other meta-analyses did not assess the impact of this factor. Our finding is consistent with that in Protégé study in which patients diagnosed < 6 weeks before random assignment showed a better C-peptide response after treatment with teplizumab in an exploratory analysis [17, 18]. Therefore, to get more effective improvement, T1D individuals might need to use the anti-CD3 mAb treatment with enough doses as early as possible.

The anti-CD3 mAb showed no effect on HbA1c level according to our meta-analysis and previous studies [20, 22]. However, our subgroup analysis suggested that early intervention (≤ 6 weeks post-diagnosis) might decrease the HbA1c level, which was reminiscent of the finding from Grando et al. that HbA1c level was reduced at the follow-up time of 6 and 12 months [21]. Although the reason for the overall insignificant improvement on HbA1c level remained to explored, the above observations suggested that the immunotherapy alone might be not enough for blood glucose control in patients with T1D. Nevertheless, the deterioration of the pancreatic β-cells is the main pathogenesis of T1D. Therefore, the critical effect of anti-CD3 mAb on the preservation of β-cells to maintain insulin secretion and reduce the exogenous insulin use could not be neglected although it hardly decreases HbA1c level.

The category of anti-CD3 mAb was not related to the efficacy according to our results. Previous clinical trials have been largely conducted on one category drug, and lack the direct head-to-head comparison between teplizumab and otelixizumab. Therefore, it is hard to evaluate their differences. However, Liu et al. reported that teplizumab showed a superior effect than otelixizumab [22]. This difference might be attributed to the variations in sample size and data analysis methods. Despite approval of teplizumab by FDA [13], its decision may be influenced not only by more clinical trials conducted on teplizumab (7 *vs.* 4 on otelixizumab in our analysis) but also by the observations indicating its capacity to delay the development of clinical T1D in non-diabetic relatives at high risk for T1D [31, 32]. Nonetheless, further research such as network meta-analysis is required to address this issue.

The reported AEs varied from different trials, leading to difficulties in classifying and summarizing the AE data to perform the meta-analysis. However, the AEs were mostly mild to moderate, and they were transient or self-limiting among the T1D subjects during the trial period [16, 17], suggestive of overall safety and tolerability. Notably, the incidence of AEs was positively correlated with the dose of anti-CD3 mAb [12]. Therefore, identifying an appropriate dose that maximizes therapeutic effects and minimizes safety risks remains a critical issue for future clinical applications.

There are several limitations in this meta-analysis. First, there were only 11 RCTs with 1093 patients with T1D receiving anti-CD3 mAb treatment. Therefore, the sample size for the meta-analysis is relatively small, which may result in limited stability of the findings and introduce potential publication bias. More RCTs with large sample size are highly needed for a more convincing conclusion. Second, the original data in some trials could not be obtained from the articles and were extracted from the GetData Graph Digitizer software. The relative statistical parameter SMD impeded our findings from entirely convey of the genuine situation of measured outcomes and might exaggerate the beneficial effects potentially. Third, the heterogeneity origin was not detected in the two endpoints HbA1c level and daily insulin requirement. Therefore, further investigation for the sources of heterogeneity is warranted. Fourth, although the cumulative dose could explain the heterogeneity of change in AUC of C-peptide, other sources of heterogeneity also warrant further investigation. Besides, it should be noted that 25 mg used in this analysis could not be applied in routine clinical practice directly. It was chosen for similar sample size distribution in two subgroups and was mainly set for the evaluation of heterogeneity source. Although our results showed that the higher dose had better β-cell function protection than the lower dose, it did not mean that 25 mg was the optimal cut-off value. Finally, the participants in the available RCTs were constrained with North America and Europe. Therefore, the multi-center trials included diverse populations were warranted.

Although our meta-analysis got the similar conclusion with others that anti-CD3 mAbs could preserve β-cell function in patients with T1D [21], our analysis showed for the first time that cumulative dose was the heterogeneity source, causing the reported different efficacies of anti-CD3 mAb in C-peptide secretion preservation. It is also the first meta-analysis assessing the impact of treatment initiation time and performing two-factor meta-regression analysis to investigate the more impactful factor. We highlighted the necessity of anti-CD3 mAb treatment with an optimal dose (probably ≥ 25 mg). Moreover, we found that earlier treatment (≤ 6 weeks post-diagnosis) and younger individuals (≤ 18 years old) would achieve more therapeutic advantages. Although approximately 193,900 dollars were needed for a 14-vial continuous regimen for the average-sized patient, making it impractical for widespread use [13], anti-CD3 mAb remained a promising therapy for T1D based on its function in protecting residual pancreatic β-cells.

Conclusion

Treatment with anti-CD3 mAb benefits T1D individuals in terms of the preservation of C-peptide response and a decrease of daily insulin requirement, especially for those who are ≤ 18 years old and receive the treatment within 6 weeks after T1D diagnosis. Importantly, enough cumulative dose of anti-CD3 mAb (≥ 25 mg) is the most critical factor that affects the efficacy of these medications. However, attention should be paid to balance the efficacy and risk of AEs in T1D individuals.

Abbreviations

AEs	Adverse events
AUC	Area under the curve
CI	Confidence interval
FDA	Food and Drug Administration
HbA1c	Glycated hemoglobin
mAb	Monoclonal antibody
RCT	Randomized controlled trial
SD	Standard deviation
SMD	Standardized mean difference
T1D	Type 1 diabetes

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12933-025-02696-7.

Additional file 1.

Additional file 2.

Acknowledgements

We thank Dr. Lin Zeng (Research Center of Clinical Epidemiology, Peking University Third Hospital) for her guidance on data processing.

Author contributions

RW, HW, and TH conceptualized, designed, and supervised the study. QW, RW, XL, and XC collected the data. QW and HW performed the data analysis. QW, RW, and TH wrote and revised the manuscript. All the authors read and approved the final manuscript.

Funding

This work was partly supported by the National Science and Technology Key Program of China (2023ZD0507000 and 2023ZD0506901), National Natural Science Foundation of China (82270843, 82170875, and 82470839), and the special fund of the National Clinical Key Specialty Construction Program, P. R. China (2023).

Availability of data and materials

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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Received: 17 December 2024 / Accepted: 18 March 2025
Published online: 29 March 2025

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