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ADMINISTRATIVE INFORMATION**Support -** No.**Review Stage at time of this submission -** Preliminary searches.**Conflicts of interest -** None declared.**INPLASY registration number:** INPLASY202540041

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 13 April 2025 and was last updated on 13 April 2025.

INTRODUCTION

Review question / Objective The novel immunosuppressant belatacept demonstrates a unique mechanism of action that significantly improves renal function and reduces metabolic complications. However, systematic evidence comparing the risk of post-transplant diabetes mellitus (PTDM) and overall safety profiles between belatacept-based regimens and calcineurin inhibitor (CNI)-based protocols remains limited.

Rationale The novel immunosuppressant belatacept demonstrates a unique mechanism of action that significantly improves renal function and reduces metabolic complications. However, systematic evidence comparing the risk of post-transplant diabetes mellitus (PTDM) and overall safety profiles between belatacept-based regimens and calcineurin inhibitor (CNI)-based protocols remains limited.

Condition being studied (1) Randomized controlled trials or prospective/retrospective cohort

studies comparing belatacept vs. CNIs (tacrolimus/cyclosporine). (2) Adult (≥ 18 years) kidney transplant recipients, regardless of donor type (living/deceased). (3) Belatacept-based regimen (either LI or MI dosing) vs. any CNI-based regimen. (4) Reported new-onset diabetes after transplantation (NODAT/PTDM) incidence, defined by: ADA/WHO diagnostic criteria, or Use of insulin/oral hypoglycemics for ≥ 30 days post-transplant, or Fasting glucose ≥ 126 mg/dL or HbA1c $\geq 6.5\%$ on two occasions. (5) Minimum follow-up of 6 months post-transplant.

METHODS

Participant or population (1) Randomized controlled trials or prospective/retrospective cohort studies comparing belatacept vs. CNIs (tacrolimus/cyclosporine). (2) Adult (≥ 18 years) kidney transplant recipients, regardless of donor type (living/deceased). (3) Belatacept-based regimen (either LI or MI dosing) vs. any CNI-based regimen. (4) Reported new-onset diabetes after transplantation (NODAT/PTDM) incidence, defined by: ADA/WHO diagnostic criteria, or Use of insulin/

oral hypoglycemics for ≥ 30 days post-transplant, or Fasting glucose ≥ 126 mg/dL or HbA1c $\geq 6.5\%$ on two occasions. (5) Minimum follow-up of 6 months post-transplant.

Intervention Belatacept [MI or LI] vs. CNIs.

Comparator Belatacept [MI or LI] vs. CNIs.

Study designs to be included RR.

Eligibility criteria Inclusion Criteria: (1) Randomized controlled trials or prospective/retrospective cohort studies comparing belatacept vs. CNIs (tacrolimus/cyclosporine). (2) Adult (≥ 18 years) kidney transplant recipients, regardless of donor type (living/deceased). (3) Belatacept-based regimen (either LI or MI dosing) vs. any CNI-based regimen. (4) Reported new-onset diabetes after transplantation (NODAT/PTDM) incidence, defined by: ADA/WHO diagnostic criteria, or Use of insulin/oral hypoglycemics for ≥ 30 days post-transplant, or Fasting glucose ≥ 126 mg/dL or HbA1c $\geq 6.5\%$ on two occasions. (5) Minimum follow-up of 6 months post-transplant.

Exclusion Criteria: (1) Case reports, reviews, editorials, or studies without a control group (CNIs). (2) Non-kidney transplants (e.g., liver, heart) or pediatric recipients. (3) No clear NODAT definition or insufficient data for risk ratio (RR)/odds ratio (OR) calculation. (4) Studies where $>20\%$ of patients received simultaneous pancreas-kidney transplants (due to inherent diabetes risk differences). (5) Overlapping cohorts (only the most comprehensive dataset was included). (6) Studies designed to evaluate CNI-to-belatacept conversion protocols compared with maintenance CNI therapy.

Information sources We systematically searched PubMed, Cochrane Library, CNKI, and EMBASE for studies published until November 30, 2024, comparing belatacept versus calcineurin inhibitors (CNIs) regarding new-onset diabetes after transplantation (NODAT) risk in kidney transplant recipients. The primary outcome was NODAT incidence. Following data extraction and quality assessment, we performed pairwise meta-analyses to compare NODAT risk between belatacept (either less intensive (LI) or more intensive (MI) regimen) and CNIs. Bayesian network meta-analysis (WinBUGS 1.4.3) was then conducted for indirect comparison between belatacept LI and MI regimens.

Main outcome(s) The LI (RR=0.65, 95% CI 0.52-0.81, $p < 0.001$; $I^2 = 30\%$) and MI (RR=0.65, 95% CI 0.52-0.81, $p < 0.001$; $I^2 = 30\%$) regimens.

Quality assessment / Risk of bias analysis

Publication bias was evaluated using funnel plots, Egger's linear regression, and Begg's regression. Funnel plots assessing the risk of new-onset diabetes after transplantation in kidney transplant recipients comparing belatacept versus calcineurin inhibitors demonstrated symmetrical distributions, suggesting absence of significant publication bias (Figure 4A, CNIs vs LI ; Figure 4B, CNIs vs MI). The analysis revealed no significant publication bias when comparing CNIs with LI or MI in kidney transplant recipients regarding the risk of new-onset diabetes. Specifically, the Begg's test yielded P-values of 0.806 (Figure 5A) for CNIs vs LI and 1.000 (Figure 5B) for CNIs vs MI. The Egger's test corroborated these findings, with corresponding P-values of 0.357 (Figure 6A) and 0.333 (Figure 6B). All results were substantially above the 0.05 significance threshold, demonstrating robust reliability of the primary analyses.

Strategy of data synthesis The geographical diversity and publication timeframe (2010–2020) of the included studies ensure the timeliness and generalizability of the conclusions. The risk of bias assessment for each study is shown in Figures 2A, B.

Subgroup analysis No.

Sensitivity analysis This study evaluated the robustness of the association between Belatacept and CNIs on the risk of new-onset diabetes in kidney transplant recipients using a leave-one-out sensitivity analysis. The results demonstrated that excluding any individual study did not significantly alter the direction or magnitude of the pooled effect size, supporting the reliability of the primary findings (Figure 7A, B).

Country(ies) involved China.

Keywords urothelial carcinoma; circulating tumor DNA; immune checkpoint inhibitors; overall survival; progression-free survival.

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