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CORRESPONDENCE

Letter to the Editor: Induction therapy as a long-term commitment: Lessons from comparative outcomes of alemtuzumab and basiliximab

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Abstract

Induction immunosuppression in kidney transplantation requires a longitudinal perspective that extends beyond early rejection prevention to encompass long-term graft durability and patient safety. In response to the recent propensity score-matched study by Chukwu *et al*, complementary considerations are provided that address two underrecognized dimensions: Cumulative immunological burden and the downstream interaction between induction strategies and maintenance immunosuppression. Potent lymphocyte-depleting agents, despite comparable short-term rejection rates, are associated with a disproportionate "immunological debt" in standard-risk recipients, manifested by increased viral complications, malignancy, impaired graft function, and inferior death-censored graft survival. In contrast, non-lymphocyte-depleting induction preserves immune competence while maintaining adequate rejection control in this population. The

integration of strict risk stratification, extended surveillance protocols, and dynamic reassessment of maintenance immunosuppression into standardized induction pathways is essential to optimize long-term outcomes. Framing induction therapy as a long-term commitment rather than a perioperative intervention supports alignment of immunosuppressive intensity with recipient risk and sustained graft stewardship.

Key Words: Kidney transplantation; Induction therapy; Alemtuzumab; Basiliximab; Graft survival; Immunological debt; Precision medicine; Patient safety

Core Tip: The choice of induction therapy in kidney transplantation has commonly been centered around short-term rejection outcomes, which do not reliably predict the long-term safety and graft outcomes. Evidence reveals that, despite similar rejection rates, alemtuzumab is associated with increased risks of infection and malignancy and reduced graft survival among standard-risk recipients. These data support a risk-stratified approach to induction therapy, advocating non-lymphocyte-depleting agents for standard-risk patients and reserving lymphocyte-depleting induction for selected high-risk recipients.

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TO THE EDITOR

We read with great interest the retrospective cohort study by Chukwu *et al*[1] which addresses a central issue in kidney transplantation: How to align induction immunosuppression with long-term graft durability and patient safety. By combining real-world clinical practice, extended follow-up, and robust propensity score matching, the authors provide evidence that is highly relevant to contemporary transplant decision-making and policy development.

Induction therapy represents one of the few immunosuppressive choices made at the time of transplantation with the potential to modulate immunologic balance and impact long-term clinical outcomes throughout the late post-transplant period[2,3]. Nevertheless, accurately defining the long-term biological consequences of different induction strategies remains challenging, as observed outcomes are modulated by recipient immunological risk, subsequent maintenance immunosuppression, and evolving post-transplant management[4,5].

While lymphocyte-depleting agents such as alemtuzumab have been adopted to reduce early rejection[6,7] and enable steroid minimization[8], their long-term biological impact remains less clearly defined outside high-immunological-risk settings, particularly when evaluated beyond short-term rejection endpoints[9,10]. The study by Chukwu *et al*[1] is therefore timely, as it shifts attention from early rejection alone, towards outcomes that ultimately define transplant success: Preserved graft function, reduced infectious and long-term graft survival.

Direct comparisons between induction agents may be challenging to interpret because alemtuzumab is often administered to recipients with higher immunologic risk[11] whereas basiliximab is more commonly used in standard-risk populations[12,13]. A key strength of the present study lies in its design, which exploits two tertiary transplant centers with distinct yet internally consistent induction strategies, thereby minimizing treatment-selection variability within each institution. This center-specific practice pattern, when combined with propensity score matching based on immunologic and transplant-related variables, allowed the construction of well-balanced cohorts with comparable baseline risk profiles. Importantly, this approach strengthens internal validity and supports the attribution of observed differences to the induction strategy itself rather than to residual baseline confounding, which is frequently observed in retrospective analyses[13,14].

Nevertheless, the retrospective nature of the analysis warrants cautious interpretation of the findings. Despite robust matching methodologies, residual confounding cannot be fully excluded, particularly in relation to unmeasured center-specific practices such as infection prophylaxis protocols, monitoring intensity, and long-term maintenance immunosuppression adjustments. These variables may influence downstream clinical outcomes and represent inherent limitations of real-world observational comparisons. Acknowledging these constraints is important when contextualizing the generalizability of the results across different transplant programs and clinical settings.

Despite that, the median follow-up period exceeding five years represents a major asset of this work and provides a robust framework for evaluating long-term outcomes related to the induction therapy literature. Such extended longitudinal observation enables clinically meaningful assessment of late-emerging outcomes, including chronic graft dysfunction, viral reactivation, post-transplant malignancy, and death-censored graft loss, which collectively reflect the cumulative biological impact of early immunosuppressive decisions[15,16]. These findings illustrate a "paradox of potency": The pursuit of early rejection avoidance through powerful lymphocyte depletion in standard-risk patients creates a disproportionate "immunological debt" that manifests in long-term safety endpoints.

To enhance clinical applicability, the concept of "immunological debt" can be translated into measurable immunological and clinical indicators. In this context, immunological debt reflects a sustained imbalance between immune suppression and immune recovery following potent induction therapy.

Relevant markers may include delayed or incomplete lymphocyte reconstitution, particularly involving CD4+ and memory T-cell subsets, persistent torque teno virus viremia as a surrogate of net immunosuppressive load, and an increased cumulative burden of clinically significant infections. Together, these parameters provide a pragmatic framework for identifying patients in whom early immunologic gains translate into disproportionate long-term biological cost[4,9,17]. These endpoints are inadequately captured in studies focused predominantly on short-term rejection metrics, despite their central relevance to long-term graft durability and patient safety.

A particularly valuable aspect of the study is its attention to the downstream interaction between induction therapy and maintenance immunosuppression, highlighting how induction choices cast a "longitudinal shadow" that constrains or reshapes long-term strategies in routine clinical practice, recipients treated with alemtuzumab frequently require deviations from their intended maintenance regimen due to cytopenias, infections, or intolerance to antiproliferative agents[17-19]. As highlighted by the authors, although alemtuzumab induction is frequently implemented within steroid-avoidance or early steroid-withdrawal protocols, a proportion of recipients do not remain steroid-free over time and require subsequent reintroduction of corticosteroids[20].

This observation underscores a key clinical insight: Induction therapy cannot be evaluated in isolation. Its true impact emerges only when considered alongside subsequent immunosuppressive modifications over time[21]. Any theoretical early immunologic advantage conferred by lymphocyte depletion is frequently offset, or even reversed, by the "reconstitution lag" and reactive treatment adaptations, which may introduce additional long-term risks.

Rather than arguing for the absolute abandonment of lymphocyte-depleting agents, the findings of Chukwu *et al*[1] provide real-world evidence supporting the importance of strict adherence to risk-stratified induction protocols. While current international guidelines[22,23] recommend tailoring induction therapy to immunological risk, clinical practice often drifts toward broader application of potent agents, including alemtuzumab, to facilitate steroid minimization or simplify perioperative management[7].

However, in high-immunological-risk recipients, non-lymphocyte-depleting induction with basiliximab may be associated with higher rates of early acute rejection when applied to recipients with high immunological risk[7,24]. In such settings, inadequate initial immunosuppression may expose the graft to early immune-mediated injury, reinforcing the need for careful recipient selection rather than uniform application of conservative induction strategies.

For immunologically matched or standard-risk recipients, such a "one-size-fits-all" approach may incur a disproportionate biological cost, whereas basiliximab appears to offer a more favorable balance between rejection prevention and preservation of long-term host defense mechanisms[25].

However, alemtuzumab remains an important therapeutic option for carefully selected high-immunological-risk recipients, where the likelihood of early aggressive rejection may outweigh the long-term hazards of immune oversuppression[6]. In contrast, the pursuit of steroid avoidance through potent induction in standard-risk patients appears potentially counterproductive, given the observed excess of infection complications and malignancy[17,19,25].

In routine clinical practice, kidney transplant recipients frequently present with overlapping and partially competing risk factors that extend beyond simplified risk categories, including recipient age and frailty, immunological sensitization, prior transplantation history, comorbidity burden, and infection susceptibility[1,11,21-23]. In these contexts, induction decisions are typically informed by consideration of the relative magnitude and long-term clinical implications of each risk domain. Immunological risk predominantly influences the likelihood of early rejection and graft injury, whereas age-related vulnerability and infection-prone profiles are more closely associated with late infectious complications, malignancy, and mortality[7,15,17]. When these factors coexist, clinical judgment requires balancing short-term graft protection against the potential for cumulative harm from excessive immunosuppression.

Consequently, the findings of Chukwu *et al*[1] offer distinct, practice-oriented directives for refining induction strategies (Table 1): (1) Standard-risk recipients: The default strategy should prioritize non-lymphocyte-depleting agents (*e.g.*, basiliximab). This approach avoids the unnecessary "immunological debt" of profound lymphocyte depletion, thereby preserving surveillance against latent viruses and neoplastic clones; (2) High-immunologic-risk recipients: Alemtuzumab should be deployed for clearly defined indications (*e.g.*, high panel-reactive antibodies, re-transplantation). However, its use mandates a paradigm shift in follow-up, requiring enhanced viral surveillance (cytomegalovirus, BK virus) that extends well beyond the conventional first post-transplant year; and (3) Longitudinal management: Clinicians must proactively anticipate the biphasic nature of risk with depleting agents: Early suppression of rejection followed by late-emerging cytopenias and immune dysregulation. Maintenance immunosuppression must be reassessed dynamically after immune reconstitution to prevent the "double hit" of chronic chemical immunosuppression layered upon a depleted immune repertoire.

Accordingly, dynamic reassessment of maintenance immunosuppression should follow a structured and time-defined approach. After lymphocyte-depleting induction, reassessment at key intervals (*e.g.*, 6 months, 12 months, and 18 months post-transplant) allows alignment of immunosuppressive intensity with evolving immune recovery[9-11,21-23].

At each stage, decision-making should integrate lymphocyte counts, virological surveillance trends, and cumulative infection history[4,16-18]. Evidence of persistent immune impairment may justify recalibration of maintenance regimens, including modulation of antiproliferative agents or calcineurin inhibitor exposure, to avoid prolonged immune dysfunction superimposed on chronic pharmacologic suppression.

Table 1 Evidence-based alignment of induction therapy with recipient risk profiles

Recipient profile	Preferred induction strategy	Clinical rationale and risk-benefit balance	Strength of supporting evidence	Mandatory clinical safeguards
Standard immunologic risk (*e.g.*, first transplant, low PRA, no DSA, well-matched donor)	Basiliximab (IL-2 receptor antagonist)	Preservation of immune competence: Prioritizes long-term safety and graft durability over absolute minimization of early steroids. Avoids profound T-cell depletion in patients with low rejection probability	Moderate-strong (retrospective cohorts, propensity-matched analyses, guideline concordance)	(1) Standard viral surveillance (cytomegalovirus, BK virus); (2) Cautious steroid minimization with close clinical monitoring; and (3) Avoidance of unnecessary maintenance immunosuppression minimization[1,2,11-14,22,23]
High immunologic risk (*e.g.*, re-transplantation, high PRA, DSA positive)	Alemtuzumab (lymphocyte-depleting agent)	Rejection prevention: Accepts higher long-term risks of infection/malignancy to prevent catastrophic early antibody-mediated or cellular rejection	Moderate (RCTs in selected populations, observational studies)	(1) Extended viral surveillance (cytomegalovirus, BK virus PCR beyond the first post-transplant year); (2) Close monitoring for cytopenias and immune reconstitution; and (3) Dynamic reassessment of maintenance immunosuppression[6,7,9,10,17-20]
Frail, elderly, or infection-prone recipients (*e.g.*, age > 65 years, prior malignancy, latent infections)	Basiliximab (conservative strategy)	Safety first: The risk of infection-related mortality or malignancy progression often exceeds the risk of graft loss due to rejection in this demographic	Weak-moderate (retrospective data, expert consensus)	(1) Strict avoidance of lymphocyte-depleting agents; (2) Enhanced malignancy surveillance; and (3) Individualized maintenance immunosuppression targets, often accepting lower trough levels[11,14,15,21,22,23]

PRA: Panel reactive antibody; DSA: Donor-specific antibody; IL: Interleukin; RCT: Randomized control trial; PCR: Polymerase chain reaction.

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