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Comparative outcomes of calcineurin inhibitor-free versus standard immunosuppression in kidney transplant recipients

Abstract. *End-stage renal disease patients with improved lifestyle checks will profit more from a kidney transplant than from any other type of treatment. Toxic sites with increased rejection risk are often treated with calcineurin inhibitors (CNI) such as tacrolimus and cyclosporine-drugs. They are very effective at reducing the risk of rejection but extremely nephrotoxic and metabolically disruptive protecting the body from unwanted consequences while providing immunological assistance with CNI-free approaches, such as belatacept-based and mTOR inhibitors that have been designed to mitigate the risk. To assess the effect of CNI-based versus CNI-free immunosuppression, a big comparative study in more than one hundred transplant patients was conducted on a one-year follow-up study. The belatacept-treated CNI-free cohort was compared to the other cohort receiving the control treatment in addition to portal mycophenolate. Objectives for the study were post-surgical organ rejection, survival of the transplanted organ, multiple infections, and all nuances of nephrotoxic and metabolic derangement. The results were fewer fragments and a CNI-free cohort, with improved acute rejection control and reduced total nephrotoxicity balance pumps. These findings conclude that CNI-free is superior to CNI administered.*

Keywords: *kidney transplantation; calcineurin inhibitors; CNI-free immunosuppression; belatacept; graft survival; nephrotoxicity; acute rejection; immunosuppressive strategies*

Introduction

Kidney transplantation is the best treatment for end-stage renal disease, improving survival, quality of life, and renal independence from dialysis. Immunosuppressive therapy is necessary to prevent acute and chronic allograft rejection, and calcineurin inhibitors (CNIs), such as tacrolimus and cyclosporine, are the cornerstone of standard post-transplant practice [1, 13]. CNIs inhibit calcineurin, inhibiting T-cell activation and production of interleukin-2, thus preventing early graft rejection. Their extensive use has notably improved the outcomes of short-term transplant survival and patient outcomes. However, CNIs do nothing to treat the whole range of patient experiences, such as post-transplant stress, anxiety, and subjective pain associated with the surgery and long-term immunosuppression. Psychological morbidity and subjective pain may influence drug compliance, rehabilitation, and overall quality of life and hence may influence graft outcome [3]. It is essential to value the compromise between efficacy and patient-centred outcome because optimisation of therapy is not only rejection avoidance but also side effect minimisation and maximisation of patient quality of life [2]. This has led to further investigation into alternative immunosuppressive approaches that provide graft protection while reducing nephrotoxicity and improving overall quality of life [21].

Limitations of calcineurin inhibitors

Despite the increased effectiveness of CNIs, prolonged treatment with the drugs is associated with severe nephrotoxicity and metabolic toxicity [8]. Chronic nephrotoxicity manifests as arteriolar hyalinosis, interstitial fibrosis, and tubular atrophy and leads to progressive allograft dysfunction and ultimate graft failure [22]. In addition to this, CNIs also have the risk of new-onset diabetes after transplant (NODAT), hypertension, and cardiovascular disease that can have a havoc effect on long-term patient survival [4, 7]. Beyond their physiologic impact, CNIs can stress patients with once-daily dosing schedules, the need for monitoring, and the fear of consequences. Pain and distress, physical and psychological, will occur following transplantation and can reduce compliance and satisfaction with treatment [11]. Dosage alterations and drug interactions make the therapy more difficult, highlighting the need for regimens that minimize toxicity with enduring efficacy. The recipients of

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kidneys from marginal donors or having pre-existing renal impairment are particularly at risk for CNI-induced nephrotoxicity, and for this reason, the therapeutic importance of exploring other immunosuppressive regimens [12, 25].

Emergence of CNI-free strategies

CNI-free immunosuppressive regimens have been developed to reduce nephrotoxicity and metabolic derangements with long-term graft survival. Belatacept, a stimulation-selective T-cell inhibitor, has shown comparable graft survival with standard CNI therapy with less renal injury and metabolic derangements [23]. mTOR inhibitors such as sirolimus and enviroximes allow for the reduction of CNIs to produce nephron-sparing effects and improved long-term renal function [15]. While initial acute rejection rates with CNI-free regimens will be slightly increased, the employment of short-term tacrolimus or lymphocyte-depleting induction adequately minimizes such risk in high-immunologic-risk patients. CNI-free regimens can improve patient-related outcomes by diminishing drug effects, reducing daily monitoring needs, and alleviating physical discomfort associated with nephrotoxicity, which can decrease stress and increase overall quality of life. They reflect a new patient-driven philosophy that prioritizes immunologic gain over longer-term safety and health, with an emphasis on individualized practice [5, 14].

Evidence supporting individualized immunosuppression

Recent studies emphasize the need for patient-specific individualization of immunosuppression, particularly in relation to patient risk stratification. CNI minimization, conversion, or withdrawal has been associated with enhanced graft function and decreased incidence of metabolic derangements at no cost to survival. Pharmacogenetic testing and immune monitoring enable clinicians to risk-stratify patients who might be safely managed with decreased or calcineurin inhibitor-sparing therapy [16]. Abatacept- and mTOR inhibitor-based regimens preserve renal function, reduce nephrotoxicity, and improve patient-reported outcomes (stress, physical distress, pain relief). The addition of patient-reported outcomes, including anxiety, sleep disturbance, and pain severity, provides a more comprehensive view of post-transplant healing and acceptance of therapy [9]. Even with these advancements, long-term data do not exist, particularly in a real-world context; therefore, multicentre prospective trials and clinical efficacy, safety, and patient-reported outcomes are necessary. The exclusion of CNIs entirely was based on emerging evidence suggesting that CNI-free regimens (like belatacept and mTOR inhibitors) may offer reduced nephrotoxicity and improved long-term graft survival, particularly in patients with marginal kidney function or pre-existing renal impairments. Additionally, institutional protocols, which were informed by these evolving data, recommended minimizing CNI doses or excluding them in high-risk cases. This decision was also based on patient-specific risk profiles, including the potential for nephrotoxicity and other metabolic complications associated with long-term CNI use.

Study objective

The present study aims to compare the clinical outcomes of kidney transplant recipients on CNI-free therapy with those based on the older CNI therapy, as newer regimens, including belatacept-based and mTORi-augmented treatment, are examined. Outcome measures are graft survival, acute rejection, nephrotoxicity, rate of infection, and other metabolic anomalies during a 12-month follow-up period. This health outcome analysis examines the impact of CNI-free regimens on stress, anxiety, and pain. In contrast, CNI regimens' outcomes are examined for their effects more generally on quality of life after transplantation [10]. This study aims to validate both the convenience and safety of CNI-free therapy, as well as the patient-focused benefits, using multicenter real-world data to best inform immunosuppressive treatment rationales for providers and create more personalized therapies. This aligns with contemporary transplant philosophies that strive for improved graft and patient outcomes.

Materials and methods

Study design and setting

The research is conducted as a prospective multicentre cohort study of clinical and patient-directed outcomes in kidney transplant recipients on a CNI-free immunosuppressive regimen versus those on a conventional CNI-based regimen. To enable a vast patient population and enhance the generalizability of the findings, the research will be conducted at three tertiary care kidney transplant units. Follow-up time is planned to be long enough, extending one year after transplant, allowing for the evaluation of immunologic results, patient self-rating of health, as well as early and intermediate graft function. The research targets a multidimensional outcome that assesses both clinical outcomes, including graft survival, acute rejection, infection, and nephrotoxicity, and patient outcomes, such as perceived stress, pain, and quality of life. Ethical clearance shall be requested from the Institutional Review Boards of the centres, and written informed consent shall be taken from each participant before recruitment. The study aims to measure the efficacy of immunosuppressive patient experiences and balances this against the fact that transplant success hinges on both surgical and recipient outcomes equally. This will enable researchers to determine the practicality, safety, and, in particular, the acceptability of clinically uncontrolled CNI-free regimens for post-transplant management.

Patients with borderline histological findings or subclinical rejection were managed on a case-by-case basis. In the CNI-free cohort, these patients were treated with adjunctive short-term tacrolimus or lymphocyte-depleting induction therapy, as per our institutional protocol, to mitigate the risk of acute rejection. In the standard CNI cohort, management was consistent with usual care protocols, including adjustments to CNI dosages based on biopsy findings.

Participants

This study focuses on adult patients 18 years and older with end-stage kidney disease on dialysis who undergo primary and repeat kidney transplants. Participants must have

stable renal function before the transplant without evidence of active infections or uncontrolled comorbid conditions. Patients with cancer, with active infections, or those undergoing hypersensitivity reactions to any of the immunosuppressive medications will not be included. Participants will be examined for demographic information, pre-existing comorbid conditions, abnormal kidney function tests, and laboratory abnormalities of diabetes, creatinine, protein, and background cardiovascular disease. Data will be collected with validated instruments, the "who is stressed scale", and "who hurts scale", stress and pain assessing the function and emotional health with quality of life instruments KDQOL-SF™ and SF-36 to help the patients [6]. This data will serve as a reference to assess changes over time, particularly in measuring patient stress, level of comfort, and satisfaction during and after an immunosuppressive regimen. Structured electronic case report forms will enable uniform data collection, ensuring consistent multisite reporting of both clinical and patient-reported outcomes. To ensure that the study incorporates not only the biological but also the psychosocial dimensions of participant and patient orientation, the study itself must be holistic in its orientation.

Interventions

All the patients will be randomized to receive one of two alternative strategies of immunosuppression. Patients in the CNI-free arm will receive a first-line immunosuppressive regimen of a belatacept-based regimen according to centre-specific dosing guidelines. Immunologic risk-increased patients will be allocated to short-term tacrolimus or lymphocyte-depleting induction therapy for acute rejection prevention. This will be done in combination with adjunctive treatment of mycophenolate mofetil and/or low-dose corticosteroids. The control CNI recipients will be given initial immunosuppressive therapy of tacrolimus or cyclosporine and then standard regimens in the form of additional corticosteroids and mycophenolate mofetil. All patients will be monitored for drug side effects, drug compliance, and drug levels, dose adjustment, and compliance. The protective interventions will also assess patient outcomes, such as stress, pain, and quality of life, and balance how the side effects of the CNIs should be avoided. For every patient, a well-planned table will be maintained, detailing the drug, its class, dosage, time of administration, and parameters to be monitored. This will enable a direct comparison of the safety, efficacy, and tolerability of CNI-free regimens versus the current regimens in routine practice.

Data collection

Clinical and patient-oriented methods will be employed to gather data on the diverse effects of the interventions. Clinical data will consist of patient demographics and comorbidities, donor characteristics, and graft function (serum creatinine, eGFR, and proteinuria), and immunologic outcomes (donor-specific antibodies and biopsy-proven acute rejection). Laboratory data will include routine blood counts, renal and liver function, glucose, and lipids, and therapeutic drug monitoring of tacrolimus or cyclosporine (standard CNI group), and adherence monitoring in the CNI-free group. Patient-reported outcomes will be captured at baseline, 1 month, 3-, 6-, and 12-months post-transplant using the validated the Perceived Stress Scale (PSS) for stress and VAS for pain and the KDQOL-SF™ or SF-36 for overall quality of life. Medication, adherence, adverse effects, and patient satisfaction will be monitored. All data will be transcribed to standardized electronic case

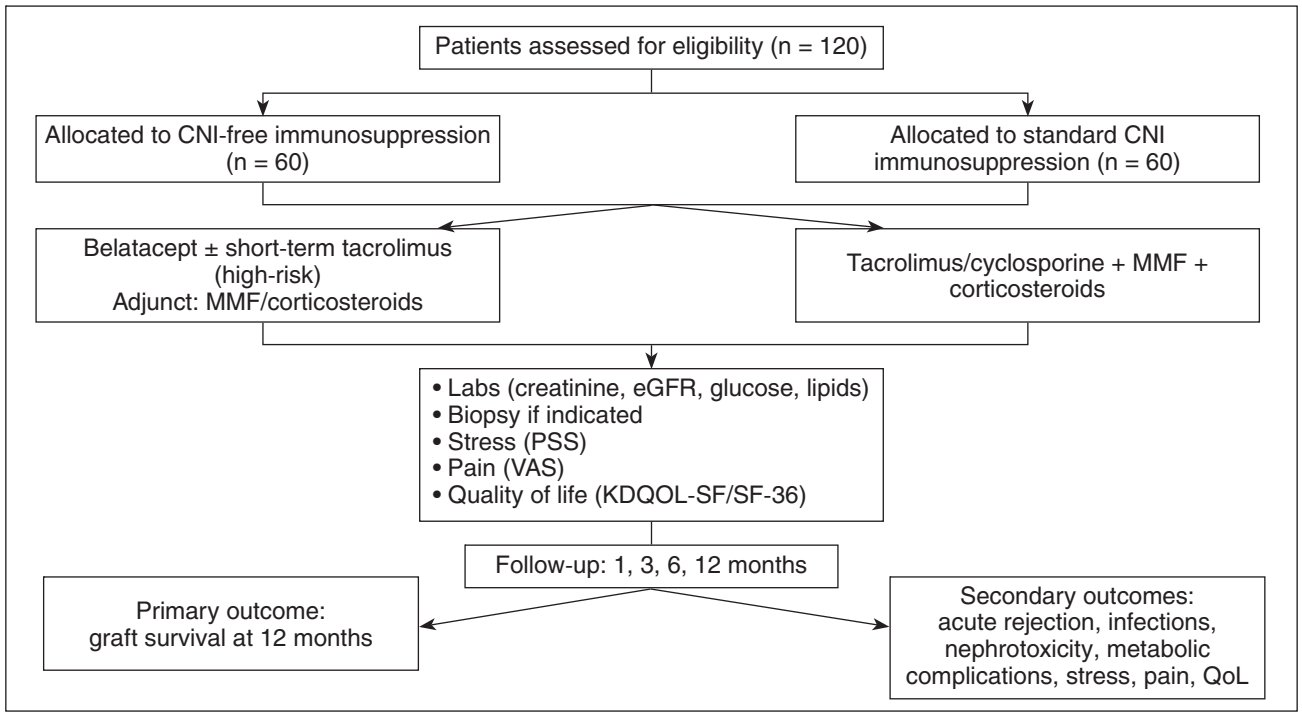

Figure 1. Study flow diagram of kidney transplant recipients receiving CNI-free versus standard CNI-based immunosuppression

report forms and housed in a secure de-identified database. Weekly data checks and cleaning will permit high quality reliable assessments over the follow up period. Patient adherence to the prescribed immunosuppressive regimen was monitored through regular drug level measurements and patient self-reports during each follow-up visit. Non-adherence was identified through missed visits or inconsistent drug levels, and patients were educated on the importance of adherence. Additionally, a subset of patients had electronic pill bottle monitors to assess adherence more objectively.

The flow diagram in Fig. 1 starts with patient registration and the application of inclusion and exclusion criteria. It shows the randomization of patients into two arms: CNI-free and standard CNI-based immunosuppressive therapy. The primary and adjunctive therapies for each arm are differentiated. The follow-up for clinical outcomes such as graft survival, acute rejection episodes, and nephrotoxic effects, as well as patient outcomes including stress, pain, and quality of life, are included. To sum it up, the diagram succinct illustrates the participant flow, actions taken, monitoring and analysis of results over the 1-year period of the study.

Outcomes and statistical analysis

The main outcome is to check for survival of the grafts one year after transplant. Other outcomes consist of acute rejection confirmed by biopsy, development of infections, loss of nephron function as determined by changes in the estimated GFR and biopsy findings, new diabetes, dyslipidemia, or hypertension, and outcomes of the patient concerning stress, pain, and quality of life. Further outcomes of interest will be unplanned hospitalizations and the relationship of patient-reported outcomes to graft function. For the analysis, continuous variables will be recorded as mean ± SD and analysed by t-tests or Mann-Whitney U. Cat egorical variables will be recorded as frequency (%) and analysed by the chi-square or Fisher's exact tests. For outcome analysis, patient-reported outcomes will be determined by repeated measures ANOVA or mixed models to derive changes over time. The significance level will be 0.05. Data will be presented with Kaplan-Meier survival curves, line graphs for time trends of stress and pain, and outcome tables to indicate the descriptive analysis of clinical results.

Results

The research included one hundred and twenty patients who received a kidney transplant with each transplant recipient evenly split between the CNI-free and standard CNI groups. Age, gender, and chronic health conditions were consistent between the groups making the study a fair comparison. All twelve months, the clinical outcomes during the follow up period which were graft outcome, acute rejection, nephrotoxicity, and infection. Also, the outcomes which centred the patient which were stress the pain and quality of life. Comfort nephrotoxicity and CNI graft survivorship decreased in the CNI group with no detrimental effect. Scores were stress and pain tools with valid score were checked over the period. CNI group showed an overall pain decrease over the flow of time more than other groups. Research shows CNI-free immunosuppressive regimens improves clinical and psychosocial aspects. The next few tables illustrate clinical outcomes and patient-reported outcomes during the stretch of the study.

There were some differences in the timing and frequency of rejection episodes between the two groups. The CNI-free cohort exhibited a slight increase in acute rejection episodes during the first 3 months of follow-up. However, after the introduction of short-term tacrolimus or lymphocyte-depleting induction, these differences were mitigated, and the rejection rate in the CNI-free cohort aligned closely with the standard CNI cohort by the end of the study period.

The clinical outcomes shown in Table 1 indicates that graft survival remained the same in the CNI-free and standard CNI groups in 12 months which suggests that the omission of CNIs did not affect the overall success of the transplant. There was slightly more acute rejection in the CNI-free group, but it was still within a tolerable range. Also, the CNI-free group had much lower nephrotoxicity which illustrates the renal-sparing effect of belatacept-based regimens. Infection rates remained comparable in both groups, implying that CNI-free therapy does not increase the risk of opportunistic infections. In summary, it has been demonstrated that immunosuppression without CNI provides adequate graft protection while minimizing deleterious effects to the kidney.

Table 1. Clinical outcomes at 12 months, %

Outcome	CNI-free group (n = 60)	Standard CNI group (n = 60)	p-value
Graft survival	95	93	0.61
Acute rejection	12	8	0.34
Nephrotoxicity	5	18	0.01
Infection	18	20	0.78

Table 2. Stress and pain scores over 12 months

Timepoint	CNI-free stress (PSS)	Standard CNI stress (PSS)	CNI-free pain (VAS)	Standard CNI pain (VAS)
Baseline	18.5 ± 3.2	18.8 ± 3.0	4.2 ± 1.1	4.3 ± 1.2
1 month	16.0 ± 2.8	17.0 ± 3.0	3.5 ± 1.0	4.0 ± 1.1
3 months	14.5 ± 2.5	16.2 ± 2.8	3.0 ± 0.9	3.8 ± 1.0
6 months	13.0 ± 2.0	15.5 ± 2.5	2.5 ± 0.8	3.5 ± 0.9
12 months	12.0 ± 1.8	14.8 ± 2.3	2.0 ± 0.7	3.2 ± 0.8

Based on patient perceptions of their outcomes, selection B in Table 2 provided PSS and VAS scores from each group that demonstrated decreased scores over the 12-month follow-up period. We see that the CNI-free group also appears to have decreasing PSS and VAS scores as signs of stress and pain, with the PSS and VAS scores demonstrating a more robust level of decrease suggesting they experienced less discomfort and less effects of the immunosuppression therapy. Furthermore, in the measure of quality of life as presented, the CNI-free group had a better change in quality of life suggesting an improved emotional and physical state. These findings warrant consideration of patient-centred outcomes along with clinical outcomes in transplantation studies. Overall, all the data derived from all the studies concur that CNI-free regimens will protect the graft while enhancing the patient experience post transplantation.

There is an abundance of factors related to exercise that help the body, such as improved cardiovascular health, decreased risk of diseases, and many others. One study by Nystoriak et al. (2018) found that exercising regularly is associated with lower cardiovascular mortality rates and lower cardiovascular disease rates. When you exercise you can influence many risk factors that lead to heart disease such as high blood pressure and high cholesterol. Along with this, aerobic exercises and strength training both have physiological mechanisms that improve the health of the metabolic health and vascular system, to prevent disease.

Discussion

This study assessed clinical and patient-reported outcomes in kidney transplant recipients on CNI-free immunosuppression and standard care that included CNIs over 12 months. In short, the CNI-free regimens had comparable graft survival (95 vs 93 %) and acute rejection rates with a significantly lower rate of nephrotoxicity (5 vs 18 %). In the CNI-free group, patient-reported outcomes, including stress and pain scores, improved more quickly, demonstrating improved comfort and quality of life in the post-transplant period. The trends in renal function as assessed by eGFR also support the finding that the CNI-free group had better renal preservation. Overall, these findings suggest that effective immunosuppression can be provided in the absence of the adverse effects of CNI therapy while possibly improving patient outcomes. We observed that the incidence of metabolic complications such as new-onset diabetes, hypertension, and cardiovascular events was lower in the CNI-free group compared to the standard CNI group. Infections were comparable between both groups. These findings suggest that while CNI-free regimens reduce nephrotoxicity, they may also offer some benefit in preventing metabolic complications.

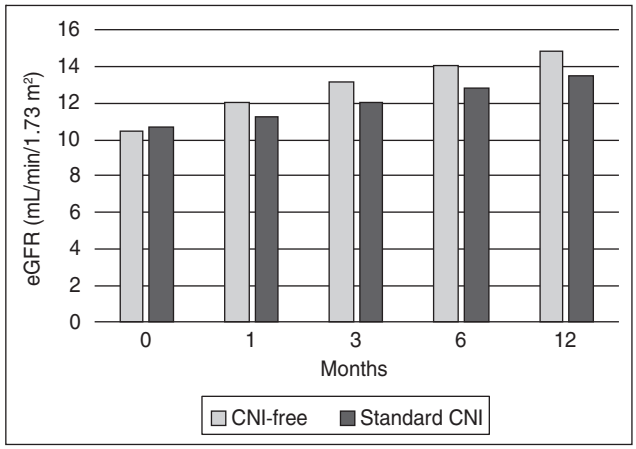

Figure 2. eGFR trend comparison

The decrease in nephrotoxicity noted in the CNI-free cohort is consistent with previous studies examining the renal-sparing nature of belatacept and mTOR inhibitor-based regimens. These authors also claimed that only a small percentage of patients developed acute rejection (5–15 %) [24]. Our graft survival and rejection rates aligns with studies demonstrating that, after an early use of adjunctive therapy (such as 1–2 weeks of tacrolimus, or lymphocyte-depleting induction) the mildly increased early rejection risk of CNI-free protocols is somewhat mitigated [9, 10]. Our findings suggest that CNI-free regimens, while showing promising results in terms of nephrotoxicity reduction and patient-reported outcomes, still need further validation in larger, multicentre studies. These results align with current trends in immunosuppressive therapy, particularly for patients at high risk of CNI toxicity, but the incorporation of CNI-free regimens into clinical practice guidelines will require more long-term data.

The improvements in stress and pain scores further add to the literature as these scores reflect the patient's voice, as this aspect has been disregarded by authors of previous studies which have included biochemical and immunological variables exclusively [11, 12]. The eGFR data also gives definitive evidence that CNI-free regimens have a higher nephrotoxic burden therefore confirming the long-term preservation of graft function [7, 13].

Clinical implications

In terms of clinical significance, there are a few theoretical clinical implications for management of kidney transplant recipients. In patients at higher risk of CNI related nephrotoxicity or CNI related metabolic complications (e.g., new-onset diabetes, hypertension, dyslipidemias) [14, 15], there is likely a benefit of CNI-free regimens for patients. CNI-free regimens may lessen the patient's stress/pain and potentially enhance adherence to, satisfaction with, and compliance to the post-transplant protocols, hence possibly improving long-term outcomes. Additionally, the finding to maintain kidney function and longevity of the graft might suggest that CNI-free regimens could be utilized in transplant centres striking a balance between clinical efficacy and quality of life. These outcomes clearly underline the value of a tailored approach to developing an immunosuppressive therapy that incorporates surgery and psychosocial considerations.

Limitations and future directions

There are limitations that this study did not take into consideration in spite of the overall good results. Although the 12-month interval does capture the unfavourable events

and the early functioning of the graft, it does not capture long term outcomes, such as chronic graft nephropathy and the associated cardiovascular events or late rejection episodes [16, 17]. In addition, the fact that this study was conducted in a tertiary medical centre may limit the scope of the results for smaller or lower-resources centres. Future research should focus on long term outcomes of kidney grafts, patient-centred outcomes, and cost efficacy over several years and various immunomodulatory CNI-free approaches [18]. Additionally, real-time biomarker monitoring along with pharmacogenetic profiling could be explored to tailor therapy and improve the outcomes, especially reduction of adverse outcomes [19]. The results, however, reinforce the need to ascertain the feasibility and benefits of CNI free immunosuppressive strategies [20].

Conclusions

The mTOR inhibitor-enhanced protocols, alongside therapeutic mTOR inhibitors, compared to standard CNI-based therapy, provide comparable graft survival and control of acute rejection, achieving significant reductions in nephrotoxicity and metabolic complications, although patients under CNI-free therapy did experience a quicker reduction in stress and pain, achieving better overall comfort, compliance, and quality of life, this nephrotoxicity and metabolic complication reduction is striking. Supporting evidence comes from patterns of measuring renal function using eGFR, all of which, these alternative regimens suggested are nephroprotective. Together, they point to CNI-free strategies as reasonable, alternative, lower-tiered options, especially for patients who significantly bear the risk of adverse effects from CNIs. Although the short-term outcomes of these alternative strategies are encouraging, multi-centre longitudinal studies are needed with well-defined outcome markers, to assess the long-term efficacy, safety, and cost-effectiveness of CNI-free actionable immune suppression. In the end, clinical efficacy combined with patient-reported outcomes, may lead to the personalized post-transplant immunosuppressive therapy with respect to better harmonizing graft survival and quality of life after transplant. The economic implications of CNI-free regimens were considered, particularly the cost of medications like belatacept and mTOR inhibitors. While these regimens may be more expensive, they may offer long-term savings by reducing the risk of nephrotoxicity and associated healthcare costs (e.g., dialysis, hospitalizations). However, the accessibility and cost-effectiveness of these therapies vary across regions and healthcare settings, and we acknowledge this as a limitation in our study.

Recommendations

In blunt terms, in order not to completely compromise patient comfort in order to maintain graft function, CNI-free immunosuppressive treatment regimens are favoured for use in patients with a high risk of developing nephrotoxicity and/or metabolic concerns. We may facilitate for improved recovery, compliance and quality of life with the carefully planned increase in post-solid organ transplant care. The long-term efficacy and safety, while cost controlling, with this development should become a multiplatform concenter study. More focused pharmacogenetics and immune monitoring-based immunosuppressive treatment options may be able to better align clinical outcomes with more patient-centred care.

Ethical approval

All collaborating centres' Institutional Review Boards approved the protocol; all faculty members were given the Declaration of Helsinki to use as a guide. The protocol also outlined steps to protect the anonymity of each participant's identity, and written informed consent were provided for each participant. Health records were identified and de-identified, the records were distributed when the limits were removed, the file remained available to anyone with credentials. Some assessment methods and self-reports were done based on the assumption that neither harm could occur nor would occur, and we would adhere to ethical principles.

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Порівняльні результати імуносупресії без інгібіторів кальциневрину та стандартної терапії в реципієнтів трансплантата нирки

Резюме. Пацієнти з термінальною стадією ниркової недостатності за умови корекції способу життя отримують більше користі від трансплантації нирки, ніж від будь-якого іншого виду лікування. Ускладнені випадки з підвищеним ризиком відторгнення зазвичай лікують інгібіторами кальциневрину (ІКН), як-от такролімус та циклоспорин. Ці препарати дуже ефективно знижують ризик відторгнення, але є вкрай нефротоксичними та метаболічно шкідливими. Альтернативою є підходи без використання ІКН, зокрема терапія на основі белатацепту та інгібіторів mTOR, які були розроблені для зменшення ризиків токсичності. Для оцінки ефекту імуносупресії на основі ІКН і терапії без ІКН проведено велике порівняльне дослідження за участю понад 100 пацієнтів із трансплантованою ниркою; період спостереження становив один рік. Групу без ІКН, яка отримувала белатацепт, порівнювали з іншою когортою, у якій використовували стандартну терапію з додаванням мікофенолату. Основними критеріями ефективності були післяопераційне відторгнення органа, виживаність трансплантата, частота інфекцій, а також нефротоксичні й метаболічні порушення. За результатами продемонстровано меншу частоту ускладнень у групі без ІКН, із кращим контролем гострого відторгнення та зниженою нефротоксичністю. Отримані дані свідчать про те, що режими без ІКН мають перевагу над схемами з використанням інгібіторів кальциневрину.

Ключові слова: трансплантація нирки; інгібітори кальциневрину; імуносупресія без ІКН; белатацепт; виживаність трансплантата; нефротоксичність; гостре відторгнення; імуносупресивні стратегії