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Comparative Efficacy and Safety of Tacrolimus Formulations

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Abstract. Tacrolimus (FK 506), a lipophilic 23-member macrolide lactone, is a potent calcineurin inhibitor immunosuppressive drug and primarily acts as acute antirejection maintenances after organ transplantation. Tacrolimus has narrow therapeutic index, large inter and intra patient variability in pharma-kinetics profile and poor oral availability due its poor solubility, which indicate hardships in determination of its optimum dose to patients. Interactions with P-glycoprotein also contributes to inconsistent therapeutic levels. There have been a lot of efforts made in different formulation of tacrolimus in order to balance between therapeutic failure and toxicity. However, generally the non-adherence to tacrolimus immunosuppressive therapy has always been associated with adverse effects. This research investigates and compares the immediate-release (IR-Tac) and extended-release (ER-Tac) formulations, focusing on their impact on patient adherence, safety, and treatment efficacy. The results indicate that ER-Tac's once-daily regimen improves adherence without compromising safety or efficacy, offering a promising alternative to the traditional twice-daily IR-Tac formulation.

Keywords: Tacrolimus; Efficacy; Safety; Comparison.

1. Introduction

Solid organ transplantation requires precise dose of immunosuppressive medications in order to prevent rejection and improve overall survival outcomes. Tacrolimus, as one of the main immunosuppressant used in kidney, liver, heart, or lung transplantation. The mechanism of action involves inhibiting calcineurin, which lead to the suppression of T-cell activation and organ rejection as a result of immune response [1]. Determining the dosing of immunosuppressant is crucial to improve long term treatment outcomes, especially post-transplant period when intra-patient variability can directly affect the clinical treatment outcomes. The intra-patient variability (IPV), which refers to the fluctuation in drugs level in patient overtime has been an emerging risk to patient and challenge to routine monitoring and frequent dose adjustment because of tacrolimus's narrow therapeutic window and varying response to IPV [1]. However, periods of overexposure and underexposure is still frequently found in patients after solid organ transplant. Tacrolimus adverse effects involve cardiac hypertrophy, hyperkalaemia, hypertension, gastrointestinal toxicity, neurotoxicity and nephrotoxicity. In addition, acute rejection of xenografts may occur from subtherapeutic tacrolimus levels. Hence, investigating into variables that impact the absorption and distribution of tacrolimus is clinically significant. Tacrolimus is recognized as a substrate for cytochrome P450 3A4 (CYP3A4), P-glycoprotein (P-gp), and a multidrug efflux transporter. As a result, any P-gp or CYP3A4 modulator may change tacrolimus's pharmacokinetics.

There are several formulations of tacrolimus developed to address with various clinical needs and to improve treatment outcomes. Different Tacrolimus formulation was also taken into account of the IPV. The formulations of tacrolimus have two main types, which is immediate-release formulation (IR-Tac), extended-release formulation (ER-Tac). IR-Tac is dosed twice on a daily basis and is indicated for the prophylaxis of organ rejection of patient undergoing solid organ transplantation. It is particularly effective in combating acute rejection in patients while it is also associated with various side effects. ER-Tac is designed for dosing once a day, which offer regimen that could possibly improve adherence and reduce the impact of IPV on patient's treatment outcome [1].

This research aims to compare and contrast the efficacy and safety of these two primary types of formulations of tacrolimus, exploring their pharmacokinetic profiles, clinical efficacy, in transplant patients. By examining the available evidence, this research will provide insights into the optimal use of tacrolimus formulations in clinical practice, helping to guide treatment decisions in solid organ transplantation.

2. Pharmacokinetics

Both once-daily formulations' pharmacokinetics (PK), safety, and efficacy have been evaluated separately with those of IR-Tac in clinical trials involving de novo and renal transplant patient conversion studies. When ER-Tac and IR-Tac are compared, it can be seen that the formulation has varying impacts on peak concentration (Cmax) and time of peak concentration (Tmax). However, ER-Tac has lower minimum concentration (Cmin) and 24-hour area under the curve (AUC24) when compared milligram for milligram. In order to obtain comparable exposure levels and troughs, ER-Tac needs a greater dosage than IR-Tac, according to clinical investigations conducted on both de novo and stable transplant patients. The addition of methylcellulose causes tacrolimus's diffusion rate to slow down, resulting in a delayed release, which is why ER-Tac offers an extended release of the drug. On the other hand, the development of LCPT was concentrated on MeltDose technology, which disperses tacrolimus in a polymeric matrix to increase its solubility and, consequently, its bioavailability. Tacrolimus is subsequently distributed further in the intestine as a result. In comparison to IR-Tac, this formulation has also been demonstrated to support more rapid attainment of therapeutic tacrolimus systemic exposure and necessitate a lower total daily dosage to reach therapeutic exposure levels. Lower peak exposure levels and less variation between the greatest exposure and trough are linked to LCPT. When compared to IR-Tac, which has a comparable safety profile, LCPT is noninferior from a clinical standpoint in terms of efficacy [2]. Among all formulation, compliance to immunosuppression treatment is prescence and is a well-recognised nonadherence factor that contributes to the adverse effect after solid organ transplantation.

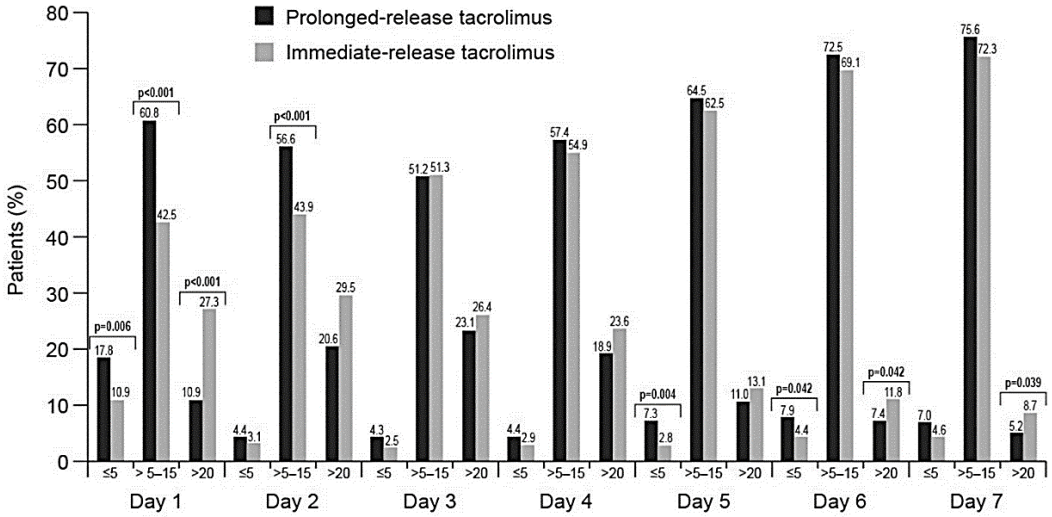

Figure 1. The proportion of patients who reach different levels of tacrolimus trough in the early stage after transplantation [3].

3. Therapeutic performance

3.1. Adherence

There is a significant proportion of patients (Figure 1), which is up to 81.8% were non-adherent to the primary composite endpoint of the tacrolimus clinical practice due to sub-therapeutic tacrolimus trough levels found in 62% of the patients [3]. The overall non-adjacent rate also exhibited no improvement throughout the change in IR-Tac to ER-Tac formulation after 12 months.

However, the collected data from the patient who experience conversion to ER-Tac from IR-Tac in different percentage (67%, 85%, and 100%) of dose of twice-daily formulation suggests that increase in adherence is positively correlated to increase in dosing frequency [1].

Patients switched from an IR-Tac to an ER-Tac formulation showed a significant improvement in medication adherence [4]. At the beginning of the study, 66.4% of patients displayed nonadherence, but this reduced to 30.9% after conversion to the once-daily regimen ER-Tac. Timing nonadherence (taking the dose late by >2 hours) also decreased from 63.6% to 27.3%.

ER-Tac is linked to improved patient adherence compared to IR-Tac regimens [5]. This is primarily due to the simplified dosing schedule. Patients find it more convenient, with 99.4% expressing a preference for the ER-Tac formulation because of reduced dosing frequency and increased convenience. Adherence improves significantly because patients are less likely to miss doses with once-daily regimens. Nonadherence rates for IR-Tac are higher, especially for the evening dose, while ER-Tac's once dosing daily simplifies medication routines and potentially reduces the risk of missed doses. A significant majority of patients expressed a preference for the once-daily formulation, citing increased convenience and improved adherence. This preference may contribute to better long-term outcomes, as adherence is a critical factor in the success of immunosuppressive therapy. While the immediate pharmacokinetic equivalence was not demonstrated, Er-Tac may improve patient adherence to medication regimens, which is crucial for long-term graft survival [6].

3.2. Safety

ER-Tac was associated with reduction in pill burden and was reported with high patient satisfaction due to improved convenience which contribute to the ease to manage their immunosuppression treatment [3]. The more frequent dosing (morning and evening) in the IR-Tac formulation led to higher rates of nonadherence, mainly due to the complexity of managing medication schedule [4]. This simplification can reduce the chance of missed doses and overall enhance the quality of life for transplant patient.

There is no evident disparity in bioavailability, safety, and efficacy properties was found in ER-Tac and IR-Tac formulation after liver transplantation [3]. Through the measurement of the rate of the treatment failure indicated by adverse effects such as acute rejection proven by biopsy, liver graft loss and death. Regarding safety, both formulations demonstrate a comparable amount of acute rejection as confirmed by biopsy [7]. Renal outcomes and number of adverse events was also reported in both formulations in a comparable manner. Moreover, measured by estimated glomerular filtration rate (eGFR), the study suggested ER-Tac has no adverse effect on renal function in comparison to IR-Tac. The overall risk ratio of graft loss, infection, adverse drug reaction, headache, backpain and blood disorder between two formulations shows no statically significant nor any meaningful difference in risk ratio. Any new safety signals were not identified in ER-Tac.

In once daily formulation, there is improvement in mean serum creatinine levels, which suggests better renal function in patients. Although pharmacokinetically sound, evening doses of tacrolimus were shown to have lower bioavailability, possibly due to circadian variations and food interactions, which may reduce drug exposure compared to morning doses.

Safety profiles of ER-Tac were similar to IR-Tac, with no increase in adverse events [4]. During the 12-month period, no episodes of acute rejection were observed, and key markers such as renal function, cardiovascular risk factors, and liver enzyme levels remained stable. Adverse events were generally mild and included issues like gastrointestinal discomfort (e.g., diarrhea and anorexia), fatigue, and minor infections, which were consistent with the known safety profile of IR-Tac. Nine patients were reconverted to the IR-Tac regimen due to adverse events like diarrhea and fatigue, but no serious safety concerns specific to the once-daily formulation emerged. Safety profiles for ER-Tac are generally comparable to IR-Tac formulations. Acute rejection rates were low (0.4%) and comparable to IR-Tac dosing regimens [5].

Renal function remained stable post-conversion, with no significant changes in serum creatinine levels or glomerular filtration rate (GFR). The study indicated no clinically relevant changes in proteinuria, blood pressure, glucose, or lipid parameters over 12 months.

Although there was a slight reduction in tacrolimus trough levels after conversion, necessitating minor dose adjustments, patients maintained stable drug exposure with low risk of nephrotoxicity. A small number of patients (1.85%) discontinued TAC OD due to adverse effects like neurotoxicity, diarrhea, or low tacrolimus levels, but these incidents were infrequent and manageable.

The conversion to once-daily tacrolimus maintained unchanged level of renal function [8], as indicated by the absence of significant changes in GFR and proteinuria over the 12-month post conversion period. This suggests that both formulations are effective in preserving kidney function in stable transplant patients. The study reported outstanding patient and graft survival rates with the once-daily formulation, comparable to those observed with the twice-daily regimen. This indicates that the once-daily formulation does not compromise the overall long-term outcomes of kidney transplantation. While the initial conversion may lead to modest reductions in tacrolimus levels (approximately 10%), the study found that after the initial adjustment period, the levels stabilized. The need for dose adjustments was minimal, with only a small percentage of patients requiring changes to maintain therapeutic levels. The overall tolerability profile of ER-Tac was similar to that of the standard formulation [9]. The study reported that no significant difference was exhibited in blood pressure, lipid profiles, or glucose levels, with very few treatment discontinuations due to adverse effects.

During the 12 months period, three patients experienced calcineurin-inhibitor-related nephrotoxicity, but this was not significantly different from what might be expected with the standard formulation. The low incidence of nephrotoxicity suggests that both formulations can be safely used in stable patients [5].

The study also noted potential benefits of ER-Tac in terms of cardiovascular risk factors. Lower peak concentrations associated with once-daily dosing may lead to improved glucose metabolism and blood pressure control, which are significant considerations given the high risk of cardiovascular abnormalities in kidney transplant recipients. The findings highlight the significance of therapeutic drug monitoring when converting from IR-Tac to ER-Tac to ensure optimal dosing and minimize variability in drug exposure [6].

3.3. Efficacy

Study reported that ER-Tac formulation is safer and has equivalent drug exposure in compared to IR-Tac [1]. The 85% ER-Tac dosing schedule provided comparable drug exposure to IR-Tac formulation without any significant increase in toxicity or adverse effects. This suggests that once-daily dosing at 85% of the total daily dose is both safe and effective for patients.

There was no significant difference in the efficacy of immunosuppression between the two dosing regimens, suggesting that the once-daily formulation is effective in maintaining adequate immunosuppression levels [4]. The results indicated that there were no significant changes in the overall effectiveness of immunosuppression after the conversion, meaning that the ER-Tac was just as effective as the twice-daily regimen, which is the IR-Tac formulation in preventing organ rejection. Trough levels of tacrolimus are measured to ensure that the drug concentration in the blood remains within a therapeutic range that is effective for immunosuppression. the researchers closely monitored these levels throughout the conversion process. In the beginning of the study, the mean tacrolimus trough level was 6.1±2.3 ng/ml. After one week of being ER-Tac formulation, this level decreased slightly to 5.5±2.1 ng/ml. This decrease indicates that, initially, the concentration of the drug in the patients' blood was lower than what was observed at the start of the study. Despite the initial decrease in trough levels, the study found that these levels tended to stabilize over time and eventually returned to baseline values during the follow-up period. This suggests that the body adjusted to the new dosing regimen, and the tacrolimus levels became consistent and effective for immunosuppression. While

there was a slight initial decrease in tacrolimus levels after switching to the once-daily formulation, the overall immunosuppressive efficacy remained unchanged, and the drug levels stabilized over time, indicating that the once-daily regimen was effective in maintaining adequate immunosuppression without compromising patient safety [10].

4. Conclusion

The transition from IR-Tac to ER-Tac has demonstrated benefits in terms of both adherence and safety, while maintaining efficacy. ER-Tac improves medication adherence due to the simplified IR-Tac formulation, which is preferred by patients over the more complex twice-daily IR-Tac regimen. This increased adherence significantly reduces the risk of missed doses and timing nonadherence, particularly for patients who struggle with evening doses. Furthermore, ER-Tac was shown to have a similar safety profile compared to IR-Tac, with no significant increase in adverse events, and stable renal and cardiovascular outcomes over time. Though some patients experienced minor adverse effects, such as gastrointestinal discomfort, the overall tolerability of ER-Tac was favorable, contributing to high patient satisfaction. Efficacy studies confirmed that ER-Tac maintains adequate drug exposure for effective immunosuppression, comparable to the IR-Tac formulation. Despite a minor initial decrease in tacrolimus trough levels after switching to the once-daily regimen, drug levels stabilized over time, ensuring effective prevention of organ rejection. Long-term outcomes, such as patient and graft survival, remained consistent between the two formulations. Overall, ER-Tac offers a more convenient and patient-friendly approach to immunosuppressive therapy, without compromising safety or efficacy, and can lead to improved long-term therapeutic outcomes in patients due to enhanced medication adherence.

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