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Evaluation of efficacy and safety of generic tacrolimus (Suprotac®) compared to reference tacrolimus (Prograf®) in kidney transplantation: a phase IV study

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Abstract

Transplant recipients are given an immunosuppressive regimen such as tacrolimus to prevent organ rejection. Suprotac® is a generic tacrolimus that is utilized in kidney transplantation regimen in Iran. This post-market study was conducted to evaluate the safety and efficacy of Suprotac® in comparison with Prograf®. In this two-armed, open-label, parallel, active-controlled, and cohort study, de novo kidney transplant recipients aging 18 to 65 years were prescribed Suprotac® or Prograf® as part of the immunosuppressant protocol. The primary outcome was comparing the mean estimated glomerular filtration rate (eGFR) at month 12. The secondary outcomes were the assessment of patient and graft survival, acute rejections during hospitalization, tacrolimus dose, trough concentration, and Trough Concentration/dose (C/D) ratio, and Adverse Events (AEs) during the study period. A total of 201 patients were enrolled in this study. At discharge, the eGFR was lower in the Suprotac® group compared to the Prograf® group (51.70 ml/min/1.73m^2 and 57.48 ml/min/1.73m^2, respectively; p=0.042). However, at month 12, there was no significant difference in mean eGFR between the two groups (58.94 ml/min/1.73m^2 and 59.78 ml/min/1.73m^2, respectively; p=0.772). Other outcomes, including patient and graft survival, acute rejection during hospitalization, tacrolimus dose, trough concentration, and C/D ratio, and overall incidence of AEs were similar between the two groups (p >0.05). The efficacy and safety profile of the generic tacrolimus were shown to be comparable to the reference tacrolimus at month 12.

Key Words: tacrolimus, kidney transplantation, estimated glomerular filtration rate, Prograf®, Suprotac®.

Kidney transplantation significantly improves the quality of life and life expectancy of individuals with End-Stage Renal Disease (ESRD).[1] The kidney transplantation rates in Iran have been estimated to exceed 2500 transplants per year.[2,3] To prevent the rejection of the transplanted organ, patients must adhere to a strict regimen of immunosuppressive medications, such as tacrolimus, an important medication in this regimen.[4]

Tacrolimus is a type of Calcineurin Inhibitor (CNI). It works by preventing the activation of T lymphocytes, which are important in the immune response and the release of inflammatory cytokines that can potentially harm the transplanted organ. When tacrolimus binds to a protein called FKBP-12, it forms complexes that bind to calcineurin. This binding inhibits the activation of T-cells and prevents the release of inflammatory mediators such as interleukin-2.[5,6]

The availability of tacrolimus, a vital component in transplant regimens, is essential for a successful kidney transplantation. Generic products play a significant role in ensuring access to these crucial medications and offer a cost-effective alternative without compromising quality. Generic tacrolimus (Suprotac®) is the generic product of the reference comparator, brand-name tacrolimus (Prograf®), and is produced by NanoAlvand Company, Iran. This cohort study aimed to evaluate the efficacy and safety of Suprotac® in comparison with Prograf® in real-world kidney transplant recipients in Iran who were prescribed tacrolimus as per routine practice.

Materials and Methods

Study design and participants

This open-label, two-armed, parallel, active-controlled, and cohort study was conducted in nine centers in Iran. The primary kidney transplant (De Novo) recipients aging 18 to 65 years were enrolled in the study. The exclusion criteria were as follows: multi-organ transplantation; receiving a kidney with a cold ischemia time of ≥12 hours; contraindication for kidney transplantation or contraindication for immunosuppressive medications of the study; calculated panel reactive antibody (cPRA) ≥30; using any other investigational drugs at the time or within 30 days of enrollment, or within five half-lives of those drugs, whichever is longer (except for dialysis-related drugs that were not expected to interact with the study regimens).

Intervention and visits

Patients received tacrolimus as Suprotac® or Prograf® in two divided doses given every 12 hours. Other medications in the transplant regimen were mycophenolate sodium/mofetil, prednisolone, with/without Anti-Thymocyte Globulin (ATG). Patients were monitored during the hospitalization following transplant surgery and underwent periodic assessments at months 1, 3, 6, 9, and 12 after the surgery.

Outcomes

The primary outcome was the mean estimated glomerular filtration rate (eGFR) at month 12 of the study. The secondary outcomes included the rate of patient survival, the rate of graft survival, biopsy-proven or clinical acute rejections during hospitalization, tacrolimus dose, trough concentration, and trough Concentration/Dose (C/D) ratio, and Adverse Events (AEs).

Safety assessments

Safety data were collected, recorded, and assessed by physicians during the study period. All AEs were classified based on the Medical Dictionary for Regulatory Activities (MedDRA Desktop Browser 4.0 Beta) terms using System Organ Class (SOC) and Preferred Term (PT).[7] All the reported events were graded according to the Common Terminology Criteria for Adverse Events version 5.0 (CTCAE v5.0).[8] Moreover, the seriousness of AEs was assessed according to ICH-E2B guidelines.[9] The causality relation was assessed based on the World Health Organization (WHO) criteria.[10]

Sample size

To assess the hypothesis of equal means of eGFR in the two study groups, 116 patients in the Suprotac® group and 58 patients in the Prograf® group (with 2:1 assignment) were needed to have a power of 95%. In a study the mean eGRF at 12th month was 62.0 (ml/min/1.73m^2) in the tacrolimus group.[11] Accordingly, the pre-assumed mean of eGRF in Suprotac® group was calculated as 52.7 (ml/min/1.73m^2) (considering to be 15% less than the tacrolimus group); and it was assumed that both groups have a Standard Deviation (SD) of 15.9.

The significance level of the test was set at 0.05, and a two-sided, two-sample equal-variance t-test was used. After accounting for a 10% missing data, it was determined that a sample size of 194 (129 in the Suprotac® group and 65 in the Prograf® group) would be necessary based on the calculated estimates. These calculations were performed using the software PASS 15 v.15.0.5.

Statistical analysis

The descriptive analysis of demographic information and efficacy outcomes involved the use of mean and SD for continuous variables. Categorical variables, on the other hand, were reported using frequency and percentage.

The primary endpoint of this study was to analyze the mean eGFR at month 12 in two groups using the Analysis Of the Covariance (ANCOVA) model. The receiving of ATG at baseline and the type of donor (living or cadaver) were used as covariates in this analysis.

In addition, the student's t-test was used to compare the mean eGFR, tacrolimus dose, trough concentration and C/D ratio at different timepoints between the two groups. The non-parametric Mann-Whitney test was used to compare Intra-Patient Variability (IPV) between the two groups and it was described using the median and inter-quartile range. Other secondary endpoints such as patient survival, graft survival, and biopsy-proven or clinically acute rejections were compared using the chi-square test between the two groups. The mean eGFR and C/D ratio were analyzed during the study time points using the Generalized Estimating Equations (GEE) model in both groups.

The safety aspect of the study was measured by calculating the incidence rate for each AE. The data was then summarized based on the PT of the AE. Patients who experienced one AE multiple times were only counted once in the incidence calculation. Additionally, a causality assessment was conducted, and its results were reported in incidence and percentage. A chi-square test was performed to compare the number of people who experienced at least one AE, at least one AE with grade 3 or higher and at least one SAE between different groups. The statistical analyses were conducted using STATA version 17.0 and R 4.2.1.

Results

A total of 201 patients were enrolled in this study, including 125 patients in the Suprotac® group and 76 patients in the Prograf® group. The demographics and baseline characteristics are shown in Table 1. The percentage of living donors was significantly lower in the Suprotac® group (p-value=0.022).

eGFR Assessments

The mean (SD) eGFR at discharge day was 51.70 (18.37) ml/min/1.73m^2 and 57.48 (20.28) ml/min/1.73m^2 in the Suprotac® and Prograf® groups, respectively (p=0.042). The mean (SD) eGFR at month 12 was 58.94 (18.65) ml/min/1.73m^2 and 59.78 (17.39) ml/min/1.73m^2 in the Suprotac® and Prograf® groups, respectively (p=0.772).
ANCOVA assessment of eGFR showed the least square means (95% confidence interval [CI]) of eGFR at month 12 were 59.7 (56.3, 63.1) ml/min/1.73m^2 and 59.2 (54.8, 63.6) ml/min/1.73m^2 in the Suprotac® and Prograf® groups, respectively (p=0.858). Moreover, the GEE model showed no significant difference between the groups (p=0.121). The longitudinal changes in eGFR and serum creatinine during the 12-month study period are shown in Figure 1.

Tacrolimus dosing, trough concentration, and C/D ratio

The mean (SD) of tacrolimus dose decreased from 6.92 (2.74) mg at discharge to 4.07 (1.89) mg at month 12 in the Suprotac® group, and from 6.40 (2.46) mg to 3.92 (1.65) mg in the Prograf® group (p=0.181 and 0.605, at discharge and month 12, respectively). The mean (SD) of tacrolimus trough concentration decreased from 7.79 (2.52) ng/mL at discharge to 7.53 (1.90) ng/mL at month 12 in the Suprotac® group, and from 7.90 (2.64) ng/mL to 7.36 (1.97) ng/mL in the Prograf® group (p=0.773 and 0.565, at discharge and month 12, respectively).
The mean (SD) C/D ratio at discharge day was 1.35 (0.82) ng/ml/mg and 1.49 (0.97) ng/ml/mg in the Suprotac® and Prograf® groups, respectively. The mean (SD) C/D ratio at month 12 was 2.48 (1.73) ng/ml/mg and 2.25 (1.28) ng/ml/mg in the Suprotac® and Prograf® groups, respectively.
The mean (SD) difference of tacrolimus dose between the discharge day and month 12 was -3.01 (3.10) in the Suprotac® group and -2.49 (2.93) in the Prograf® group (p=0.579). Similarly, the mean (SD) difference of tacrolimus trough concentration between the discharge day and month 12 was -0.43 (2.72) in the Suprotac® group and -0.55 (2.53) in the Prograf® group (p=0.829). Furthermore, the mean (SD) difference of C/D ratio between the discharge day and month 12 was 1.16 (1.58) in the Suprotac® group and 0.78 (1.18) in the Prograf® group (p=0.617).
The means and standard errors of C/D ratio (ng/ml/mg) trend from discharge to month 12 are demonstrated in Figure 2. The mean tacrolimus C/D ratio significantly increased over time ($p < 0.001$) and there was no significant difference between the groups (p=0.291).
The trough concentrations at months 3, 6, 9, and 12 were used for the assessment of IPV. The median (Q1, Q3) IPV was 17.92% (9.23, 27.18) and 18.70% (10.37, 26.27) in the Suprotac® and Prograf® groups, respectively (p=0.712).

Table 1. *Patients' demographics and baseline characteristics.*

Variable	Suprotac® (N=125)	Prograf® (N=76)
Gender (Female)	47 (37.60)	23 (30.26)
Age (Year)	40.88±11.39	41.43±11.69
Weight (kg)	70.26±13.97	68.15±15.52
Current smoking	8 (6.40)	4 (5.26)
Current alcohol consumption	4 (3.20)	2 (2.63)
Donor (Living)	50 (40.00)	43 (56.58)
Received ATG[a]	69 (55.20)	42 (55.26)

Data in this table are number (% of total participants in the treatment group) or mean±standard deviationa.
[a]ATG, anti-thymocyte globulin.

Acute rejection during the hospitalization, graft survival, and patient survival

During the hospital stay after surgery, a total of 16 transplant rejections occurred; nine in the Suprotac® group (three based on biopsy and six with clinical criteria) and seven in the Prograf® group (three based on biopsy and four with clinical criteria). However, there was no significant difference between the two groups (p=0.610). Out of the 16 rejections, three graft losses occurred, with one in the Suprotac® group and two in the Prograf® group (p=0.306). During one year follow-up, similar graft survival rates were found in both groups, with 116 (92.8%) and 70 (92.1%) patients in the Suprotac® and Prograf® groups, respectively (p=0.855). Additionally, 118 (94.4%) patients in the Suprotac® group and 72 (94.7%) patients in the Prograf® group survived, with no significant difference found between the two groups (p=0.928). The total graft and patient survival were 92.5% and 94.5%, respectively.

Safety results

Among all patients, 27.20% in the Suprotac® group and 38.16% in the Prograf® group experienced at least one AE

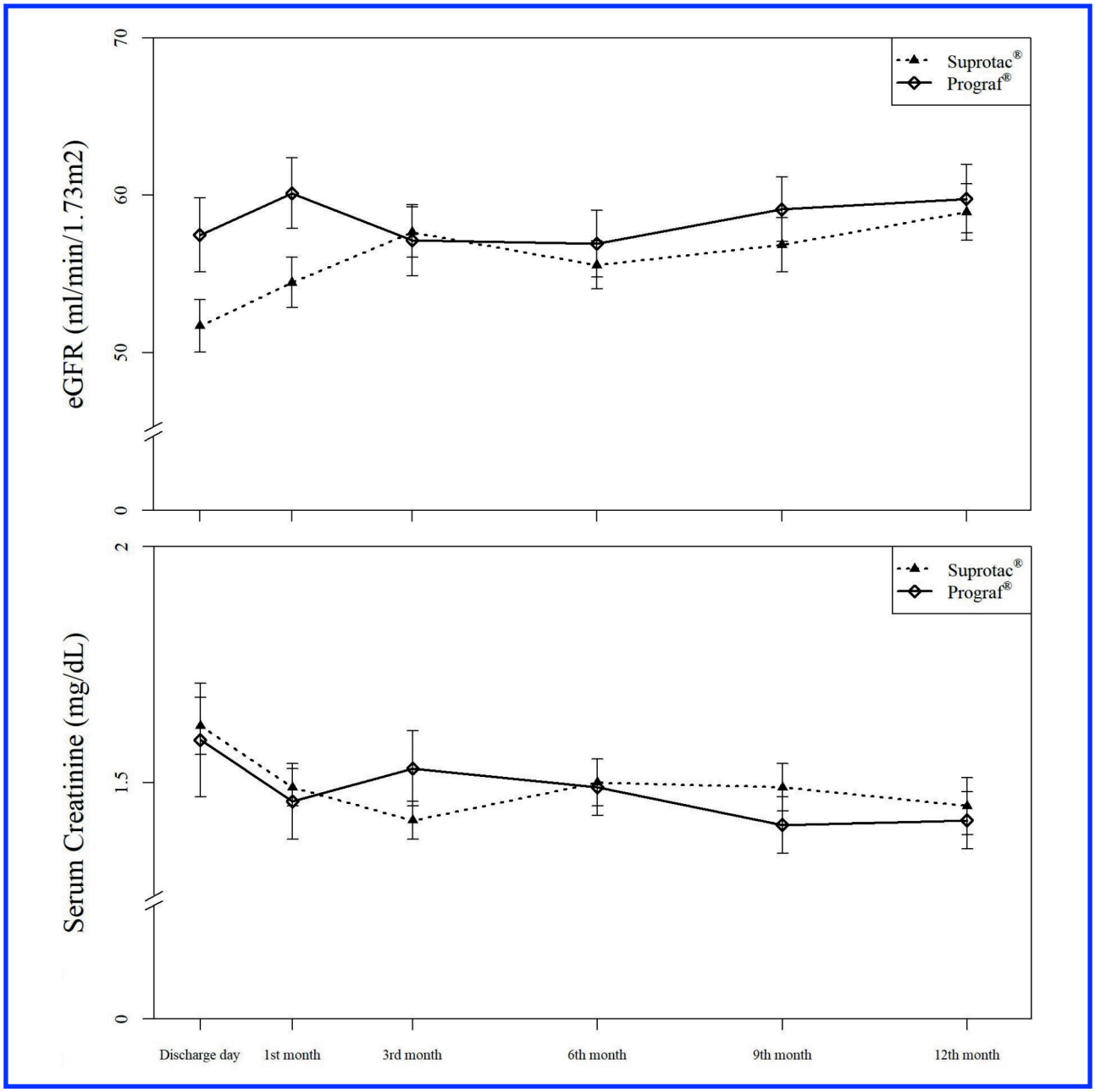


Figure 1. *Longitudinal changes in eGFR and serum creatinine during the study period (mean±standard error). eGFR, estimated glomerular filtration rate.*

(p-value=0.104). The most common reported PTs in both groups were "coronavirus infection" and "infection", respectively.

Regarding severity, 26/125 (20.80%) patients in the Suprotac® group and 23/76 (30.26%) patients in the Prograf® group experienced at least one AE with grade three or higher (p-value=0.130). Furthermore, 22/125 (17.60%) patients in the Suprotac® group and 18/76 (23.68%) patients in the Prograf® group experienced at least one Serious Adverse Event (SAE) (p-value=0.295). SAEs predominantly resulted in "in-patient hospitalization or prolongation of existing hospitalization". Further details regarding the reported AEs are shown in Table 2.

With respect to the causal relationship to the study intervention, 30 (24.00%) patients in the Suprotac® group and 24 (31.58%) patients in the Prograf® group experienced at least one AE that was at least possibly related to the intervention. Additionally, 15 (12.00%) patients in the Suprotac® group and 13 (17.11%) patients in the Prograf® group reported at least one SAE with at least possible causal relation to the study intervention.

Discussion

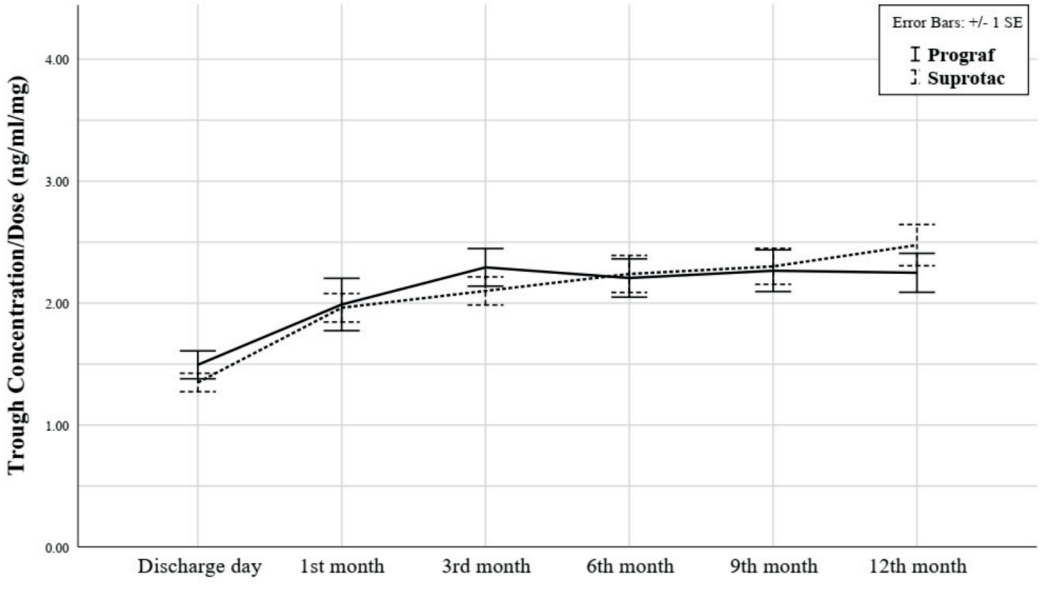
According to the findings of this study, the mean eGFR and other efficacy parameters including graft and patients' survival were comparable between the Suprotac® and Prograf® groups after 12 months of treatment. Moreover, there was no significant difference regarding safety profile between the two groups.

In this study, the mean eGFR of patients was comparable to that of other studies, indicating appropriate kidney function in transplant recipients. In a Spanish study on a large population of transplant recipients, the greatest number of patients had an average annualized eGFR of 51.4 mL/min/1.73 m^2.[12] In another study comparing a generic tacrolimus with Prograf® in renal transplant recipients, the mean eGFR in the Prograf® group was 54.3 mL/min/1.73 m^2 after six months.[13]

The graft (92.5%) and patient (94.5%) survival outcomes in this study were consistent with the results of previous trials. A study evaluating the long-term outcomes of kidney transplants showed a 1-year graft survival of 94.3% and 97.8% in recipients with deceased and living donors, respectively.[14] In a systematic review, the 1-year graft and patient survival rates among Iranian transplant recipients were 92.48% and 91.27%, respectively.[15]

A large-scale study in Korea revealed that the rate of acute rejection during hospitalization decreased from almost 17% in 2002 to 6% in 2017.[16] The later years' results aligned with the percentage of acute rejection observed in our study.

The previous studies have shown that patients with a C/D



	Discharge day	1st month	3rd month	6th month	9th month	12th month
Trough concentration/dose (ng/ml/mg)						
Suprotac®	1.35	1.96	2.10	2.24	2.30	2.48
Prograf®	1.49	1.99	2.29	2.21	2.27	2.25
P-value	0.271	0.914	0.311	0.886	0.878	0.330

Figure 2. *The mean of tacrolimus trough concentration/dose (ng/ml/mg) during the study.*

Table 2. *Safety results the reported AEs.*

	Suprotac® (N=125)[a]	Prograf® (N=76)[a]
Number of patients with at least one AE[b] (P-value: 0.104)	34 (27.20)	29 (38.16)
AEs ≥3%[c]		
Corona virus infection	6 (4.80)	6 (7.89)
Infection	5 (4.00)	5 (6.58)
Blood creatinine increased	2 (1.60)	6 (7.89)
Polyomavirus test positive	4 (3.20)	4 (5.26)
Hyperglycaemia	5 (4.00)	1 (1.32)
Myocardial infarction	1 (0.80)	3 (3.95)
Patients with at least one AE with grade 3 or higher (P-value=0.130)	26 (20.80)	23 (30.26)
Patients with at least one SAE[d] (P-value=0.295)	22 (17.60)	18 (23.68)

Data in this table is presented as incidence (% of total participants in safety analysis set).
[a]Safety analysis set; [b]AE, adverse event; [c]adverse events which reported in more than 3% of patients in either group; [d]SAE, serious adverse event.

ratio of more than 1.05 ng/mL/mg at month 3 after transplantation are slow metabolizers of tacrolimus.[17,18] Based on the results of the present and previous studies, it appears that most Iranians are slow metabolizers.[19,20] Despite the reduction in tacrolimus dosage over time, the C/D ratio increased gradually in this study. This may be due to the decreased activity of metabolizing enzymes and the decline in tacrolimus clearance, as observed in the study by de Jonge *et al.*[21].The dosing and trough concentration of tacrolimus, the C/D ratio, and IPV results were not statistically different between the two groups and were similar to previous studies.[22-25]

Since this study was conducted during COVID-19 pandemic, the most common reported AE was "coronavirus infection", followed by unspecified infections. A study by Kim *et al.* reported upper respiratory tract as the most frequently reported site of infection (8.5%).[26]

Hyperglycemia is a common complication following transplantation and could represent the initial stage in the development of post-transplant diabetes mellitus (PTDM).[27] Heisel *et al.* observed a hyperglycemia incidence of 15.4% in patients treated with tacrolimus. In the current study, "hyperglycemia" was among the frequently reported AEs.[28]

Based on the safety data obtained in this study, and considering the overall incidence of AEs and those classified as grade 3 or higher, it appears that Physicians predominantly reported only the more severe AEs or SAEs. As highlighted by Dalia Jacob *et al.* and Muaed Alomar *et al.* in their studies, under-reporting is a major limitation of post-market surveillance studies. According to these studies, severity and seriousness of AEs as well as the required time for physicians to report them, are among the most common contributing factors.[29,30] Additionally, the Weber effect represents a well-known bias in AE reporting. It is characterized by a decrease in AE reports after the initial years of a drug's regulatory approval, which is attributed to a decline in the reporting of clinically mild or trivial reactions.[31] Consequently, these factors can lead to non-reporting or under-reporting of known and well-established AEs.

Conclusions

Overall, the findings of this study suggest that tacrolimus is well tolerated among kidney transplant recipients, with no safety concerns that stand out compared to similar studies. Furthermore, Suprotac® and Prograf® demonstrated comparable safety profiles. According to these results, the efficacy and safety of Suprotac® were comparable to those of Prograf® in kidney transplant patients.

List of abbreviations

eGFR, Estimated glomerular filtration rate
C/D, concentration/dose
AEs, adverse events
PTDM, post-transplant diabetes mellitus
SAE, serious adverse event
CI, confidence interval
ANCOVA, analysis of the covariance
IPV, intra-patient variability
GEE, generalized estimating equations
SOC, System Organ Class
PT, Preferred Term
CTCAE v5.0, Common Terminology Criteria for Adverse Events version 5.0
WHO, World Health Organization
ESRD, end-stage renal disease

CNI, calcineurin inhibitor
Suprotac®, Generic tacrolimus
Prograf®, brand-name tacrolimus
cPRA, calculated panel reactive antibody

Ethics approval

The study was approved by the local ethics committee of Baqiyatallah University of Medical Sciences (IR.BMSU.REC.1399.375). All experiments were performed in accordance with relevant guidelines and regulations such as the Declaration of Helsinki and the participants signed the informed consent form and agreed to be published.

Informed consent

All patients participating in this study signed a written informed consent form for participating in this study.

Availability of data and materials

The datasets used and/or analyzed in the present study are available from the corresponding author upon reasonable request.

Conflict of interest

The authors declare no competing interests.

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Authors' contributions

All authors participated the draft, design, supervision, editing, analysis, writing, and data interpretation. All authors read and approved final manuscript.

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