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ABOUT COVER

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AIMS AND SCOPE

The primary aim of *World Journal of Transplantation* (*WJT*, *World J Transplant*) is to provide scholars and readers from various fields of transplantation with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJT mainly publishes articles reporting research results obtained in the field of transplantation and covering a wide range of topics including bone transplantation, brain tissue transplantation, corneal transplantation, descemet stripping endothelial keratoplasty, fetal tissue transplantation, heart transplantation, kidney transplantation, liver transplantation, lung transplantation, pancreas transplantation, skin transplantation, *etc*.

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MINIREVIEWS

Impact of tacrolimus intra-patient variability in adverse outcomes after organ transplantation

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Abstract

Tacrolimus (Tac) is currently the most common calcineurin-inhibitor employed in solid organ transplantation. High intra-patient variability (IPV) of Tac (Tac IPV) has been associated with an increased risk of immune-mediated rejection and poor outcomes after kidney transplantation. Few data are available concerning the impact of high Tac IPV in non-kidney transplants. However, even in kidney transplantation, there is still a controversy whether high Tac IPV is indeed detrimental in respect to graft and/or patient survival. This may be due to different methods employed to evaluate IPV and distinct time frames adopted to assess graft and patient survival in those reports published up to now in the literature. Little is also known about the influence of high Tac IPV in the development of other untoward adverse events, update of the current knowledge regarding the impact of Tac IPV in different outcomes following kidney, liver, heart, lung, and pancreas tran-splantation to better evaluate its use in clinical practice.

Key Words: Tacrolimus; Intra-patient variability; Rejection; Organ transplantation; Graft survival; Outcomes

Core Tip: Tacrolimus is widely used after solid organ transplantation. High intra-patient variability of tacrolimus (Tac IPV) has been associated with poor graft and patient survival. This review summarizes current evidence regarding the impact of high Tac IPV in several outcomes after kidney, liver, heart, lung and pancreas transplantation.

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INTRODUCTION

Tacrolimus (Tac) is nowadays the most common immunosuppressive drug employed in solid organ transplantation and has replaced cyclosporin as the most common calcineurin inhibitor used worldwide in immunosuppressive regimens[1, 2]. Tac exhibits a peculiar pharmacokinetic profile with large inter-patient and intra-patient variability (IPV) of whole blood drug levels over time, even when doses remain unchanged. This is usually ascribed to overlapping factors, such as ethnicity, pharmacogenomics, food-drug and drug-drug interactions, non-adherence, enhanced Tac absorption or impaired drug excretion due to either diarrhea or cholestasis, assays variability for Tac levels determinations or even alternate use of Tac compounds or its generic formulations[3-5]. Due to its narrow therapeutic window, therapeutic drug monitoring of trough levels (Cmin) is required to attain target levels of immunosuppression over time, as well as avoidance of undesired Tac side effects such as infections, neurotoxicity and nephrotoxicity, which are usually related to higher drug exposure[1].

High Tac IPV or time in the therapeutic range (TTR) of Tac has been associated with an increased risk of immune-mediated rejection and poor outcomes after kidney transplantation (KT)[5,6]. Few data are available concerning the impact of high Tac IPV in non-kidney transplants[7]. However, even in KT, there is still a controversy whether high Tac IPV is indeed detrimental in respect to graft and/or patient survival[5,6]. This may be due to different methods employed to evaluate IPV and distinct time frames adopted to assess graft and patient survival in the reports published up to now. Little is also known about the influence of high Tac IPV in the development of other harmful adverse events associated with immunosuppression, such as infections, chronic kidney disease, type 2 diabetes, metabolic syndrome and *de novo* or recurrent cancer. The purpose of this review is to provide an update of current knowledge regarding the impact of Tac IPV in different outcomes following KT, liver (LT), heart (HT), lung, kidney/pancreas and bone marrow (BMT) transplantation to better evaluate its use in clinical practice.

STUDY SELECTION

To identify and select studies for this review, research was made in the MedLine/PubMed database, using the following terms: Tacrolimus; intra-patient; variability; transplant; transplantation; rejection; and graft loss. These terms were obtained from Medical Subject Headings (MeSH), using the Booleans "AND" and "OR", from various search algorithms in PubMed.

Search 1: ((“tacrolimus”[MeSH Terms] OR “tacrolimus”[All Fields]) AND “intra”[All Fields] AND (“patient s”[All Fields] OR “patients”[MeSH Terms] OR “patients”[All Fields] OR “patient”[All Fields] OR “patients s”[All Fields]) AND (“variabilities”[All Fields] OR “variability”[All Fields] OR “variable”[All Fields] OR “variable s”[All Fields] OR “variables”[All Fields] OR “variably”[All Fields])) AND (y_10[Filter]). Search 2: ((((((tacrolimus[Title/Abstract]) AND (variability[Title/Abstract])) OR (intrapatient variability[Title/Abstract])) AND (transplant[Title/Abstract])) OR (transplantation[Title/Abstract])) AND (rejection[Title/Abstract])) OR (graft loss[Title/Abstract]).

Subsequently, an active manual search of studies was carried out through carefully selected articles in gray literature.

The research was completed on May 17th, 2023. A total of 43 articles were included in the present study, 376 studies were found in PubMed database, and after careful reading of abstracts, 15 were included in our final review (references No. 3, 7, 24, 31, 33, 37, 38, 57, 60, 62, 65-67, 69, and 70). The excluded works did not satisfactorily meet the theme proposed for the present work. Furthermore, 28 studies different from the ones previously selected in PubMed database were identified in our active manual research in gray literature, all of which were included in this review.

METHODS USED TO ASSESS TAC IPV

Intra-patient variability of Tac over time has been calculated using different methods, particularly[5-7]: Mean levels and standard deviation (SD) of Tac whole-blood Cmin levels, also expressed as the medication level variability index (MLVI).

Mean absolute deviation (MAD), based on the formula MAD (%) = {[(Xmean - X1) + (Xmean - X2)… + (Xmean - Xn)]/n of Cmin results}, where X is the Tac Cmin level.

Coefficient of variation (CV), calculated according to the formula CV (%) = σ/μ, where σ is the standard deviation, and μ is the mean Tac Cmin levels of all available samples of the individual. CV may be corrected or not by the corresponding Tac dose (C0/D) or defined as time-weighted coefficient of variability using time-weighted standard deviation divided by the mean drug levels.

Tac TTR, calculated by the Rosendaal method[8]. Standard deviation or MLVI are expressed as numbers, classes, or dichotomized intervals, whereas CV and TTR are expressed as percentages, tertiles and dichotomized intervals usually at the median split. There are no universally accepted recommended target levels for each one of those parameters used to assess Tac IPV. It is important to highlight that target levels of Tac Cmin usually vary over time according to the type of organ transplant, donor and recipient risk factors for rejection, comorbidity, occurrence of side effects and local immunosuppression protocols. The TTR may also vary sharply according to adopted Tac Cmin thresholds used by distinct centers in different time frames after organ transplantation[5-7].

FACTORS INFLUENCING TAC IPV

Interpatient variability of Tac has been attributed to interindividual pharmacokinetics variability which may be induced by several factors including drug-food and drug-drug interactions, concurrent clinical events such as diarrhea, cholestasis or liver dysfunction, ethnicity and pharmacogenetics[3,9-13]. In this regard, polymorphisms in CYP3A5, CYP3A4, and SLC and ABC transporter encoding genes have been shown to influence the area under the curve of tacrolimus, leading either to rejection or even toxicity in transplant recipients[4,13].

Tac IPV, on the other hand, has been additionally ascribed to non-adherence after organ transplantation, pre-analytical and analytical variables to measure Cmin in different commercially available biochemical assays and administration of different Tac formulations, including generic substitutions[3,5-7]. However, non-adherence is a common reason reported in medical literature to explain the observed deleterious effect of Tac IPV on patient and graft survival in organ transplantation by some[14-19], but not all authors[20,21].

Several approaches have been proposed to assess IPV, with most studies being retrospective, with different methodologies, considering pediatric and adult populations, with no organ-specific approach. Despite these limitations, IPV provides a sign that patients are at risk.

TAC IPV IN HEART TRANSPLANTATION

Four studies evaluating the influence of Tac IPV on HT outcomes were performed in adult patients using Tac CV[22-24] and Tac TTR[25], and in pediatric subjects using Tac SD/MLVI[26,27].

Concerning pediatric LT, Pollock-Barziv *et al*[26] associated Tac IPV with late rejection as well as worse patient and graft survival, but it is worth to mention that few heart transplant recipients were included in this study. Sirota *et al*[27] found similar results for rejection, but the authors also linked Tac SD/MLVI, particularly when higher than 3, to cardiac allograft vasculopathy and patient survival. In adults, Gueta *et al*[22] described an association of Tac IPV in the first year after HT with rejection after 12 but not between three and 12 mo after HT. On the other hand, Shuker *et al*[23] found no increase in the frequency of either early or late acute rejection or even cardiac allograft vasculopathy in heart transplant recipients. Both authors ascribed the lack of association of Tac IPV with early acute rejection[20] and overall rejection[23] to a higher immunosuppression exposure frequently observed in those heart transplant recipients. González-Vílchez *et al*[24] studied the largest cohort up to now. The authors found an effect of Tac IPV, assessed between four to 12 mo after HT, on the frequency of rejection after one year. Using Tac TTR, Baker *et al*[25] found no effect of Tac IPV on acute rejection within the first 30 d after HT. None of those studies in adults reported other outcomes such as mortality or Tac-related adverse events in association with Tac IPV[22-25]. The main findings related to HT are depicted in Table 1[22-27].

TAC IPV IN LUNG TRANSPLANTATION

Four studies have investigated the impact of Tac IPV in the frequency of acute and chronic rejection or chronic lung allograft dysfunction (CLAD) after lung transplantation in adults using Tac SD/MLVI[28], Tac CV[29] and Tac TTR[29-31]. Gallagher *et al*[28] demonstrated that higher Tac SD/MLVI between 6-12 mo after lung transplantation was associated with development of CLAD with an adverse impact on survival. Acute rejection, on the other hand was not associated with Tac SD/MLVI[28]. Ensor *et al*[30] evaluated retrospectively the role of Tac TTR in 292 Lung transplant recipients the development of acute and chronic rejection. Tac TTR was measured in the first year after lung transplantation. The authors observed a lower likelihood for acute rejection and CLAD whenever Tac TTR was increased by 10%. Lower rates of infection and mortality was also linked to high Tac TTR. Other authors failed to demonstrate higher frequency of acute rejection after lung transplantation when Tac IPV was assessed by either Tac CV or Tac TTR in the first 6 mo after surgery[29]. On the other hand, more recently Japanese investigators disclosed an association of acute rejection with Tac TTR calculated in the first six month after lung transplantation[31]. The main findings related to lung transplantation are depicted in Table 2.

Table 1 Tacrolimus intra-patient variability in heart transplantation: Main findings

Heart transplantation				
Ref.	**Sample size**	**Donor type**	**Tac-IPV, assessment**	**Outcome**
Gueta *et al*[22], 2018	72	Deceased	CV	High trough level variability is associated with higher rates of graft rejection, and trough level variability during the first year is associated with increased risk of rejection after HT
Shuker *et al*[23], 2018	86	Deceased	MAD	A high IPV was not associated with the development and progression of cardiac allograft vasculopathy or development of acute cellular rejection
González-Vílchez *et al*[24], 2022	1581	Deceased	CV	IPV levels had limited influence on mid-term outcomes in heart transplant, however high IPV may predispose to rejection in initially stable patients
Baker *et al*[25], 2019	67	Deceased	TTR	Higher TTR was not associated with a lower rate of Acute Cellular Rejection within the first 30 d after heart transplant
Pollock-Barziv *et al*[26], 2010	144	Deceased	SD	Associated Tac IPV with late rejection as well as worse patient and graft survival, but it is worth to mention that few heart transplant recipients were included in this study
Sirota *et al*[27], 2021	118	Deceased	SD	SD ≥ 3 is associated with increased risk of poor outcomes

CV: Coefficient of variability; HT: Heart transplant; MAD: Mean absolute deviation; TTR: Time in therapeutic range; SD: Standard deviation.

Table 2 Tacrolimus intra-patient variability in lung transplantation: main findings

Lung transplantation				
Ref.	**Sample size**	**Donor type**	**Tac-IPV assessment**	**Outcome**
Gallagher *et al*[28], 2015	110	Non specified	SD	Patients with highly variable trough tacrolimus levels in the second half of the first post-transplant year will likely have similar variability in the second year and are at high risk for subsequent chronic lung allograft dysfunction and death
Kao *et al*[29], 2021	157	Non specified	CV and TTR	The results suggest that tacrolimus TTR, time in therapeutic range, and variability are not related to the presence of ACR in LTRs
Ensor *et al*[30], 2018	292	Non specified	TTR	Tacrolimus TTR was predictive of clinical outcomes of ACR, CLAD, infection, and death in lung transplant recipients at 1 yr in this investigation after adjusting for potential confounders
Katada *et al*[31], 2022	90	Living and deceased	TTR	A lower tacrolimus TTR is a predictor of late acute rejection

SD: Standard deviation; TTR: Time in therapeutic range; ACR: Acute cellular rejection; LTR: Lung transplant rejection; CLAD: Chronic lung allograft dysfunction.

TAC IPV IN LIVER TRANSPLANTATION

Impact of Tac IPV on different outcomes after LT, including allograft rejection, postoperative complications and survival was evaluated in pediatric[26,32-35] and adult[36-42] transplant recipients using SD/MLVI[26,32-34], CV[35-41], and TTR [42].

Most studies performed in children associated higher SD/MLVI to biopsy-proven acute rejection (BPAR) at least six months after LT[42-34]. Defrancq *et al*[35] found similar results in another cohort of children using Tac CV one year after surgery. The authors reported an association between high Tac CV and BPAR and correlated Tac CV with albumin and bilirubin levels in different time frames after LT as well as with missed outpatient consultations, possibly reflecting immunosuppression adherence[33]. Decreased survival was also related to high Tac IPV in just one of those reports including few patients submitted to LT[26].

Up to now, seven reports were published in the medical literature concerning the effect of Tac IPV on post-LT outcomes in adults. In this regard, Christina *et al*[36] disclosed an association between Tac SD/MLVI and BPAR in patients submitted to LT. Similar findings were reported by Del Bello *et al*[37] who reported higher Tac CV measured just after LT discharge with BPAR, as well as with the occurrence of *de novo* anti-donor specific antibodies (*dn*DSA). No impact was seen in patient survival[37]. Van der Veer *et al*[39] evaluated the influence of Tac CV measured between six to 18 mo after LT in adult subjects. The authors were unable to disclose any association between Tac CV and immune mediated graft injury. Rayar *et al*[38] investigated the influence of Tac CV measured in the first 30 d after LT on postoperative outcomes. The authors found an increased frequency of acute kidney injury as well as cardiovascular and

Table 3 Tacrolimus intra-patient variability and liver transplantation: Main findings

Liver transplantation				
Ref.	**Sample size**	**Donor**	**Tac-IPV assessment**	**Outcome**
Lieber *et al*[18], 2013	988	Not specified	SD	Non-adherence among liver transplant recipients is associated with increased risk of graft failure
Stuber *et al*[19], 2008	96	Not specified	SD	The SD has utility of monitoring routine tac blood levels in pediatric recipients for detecting non-adherence prior to clinical rejection
Venkat *et al*[32], 2008	101	Not specified	SD	Variations in tac blood levels is associated with an increased risk of late allograft rejection in pediatric recipients
Shemesh *et al* [33], 2017	400	Both living and deceased donor	SD; MLVI	MLVI predicts late acute rejection in pediatric liver transplantation recipients
de Oliveira *et al* [34], 2017	50	Both living and deceased donor	SD; MLVI	MLVI may be a nice indicator of the risk of medication non-adherence in child-age
Defrancq *et al* [35], 2019	41	Both living and deceased donor	CV	High Tac IPV may be associated with adverse patient outcomes. Also, there is some impact of biological factors on IPV and therapy adherence
Christina *et al* [36], 2014	150	Not specified	SD; MLVI	The MLVI is associated with and can predict rejection, possibly related to non-adherence in adult recipients
Del Bello *et al* [37], 2018	116	Deceased donor only	CV	Tac IPV could be useful to identify patients with a greater risk of graft rejection and pf developing *de novo* DSA after liver transplantation
Rayar *et al*[38], 2018	812	Deceased donor only	CV	High CV of Tac concentrations was found to be predictive of Tac-related toxicity and poorer survival
van der Veer *et al* [39], 2019	326	Both living and deceased donor	CV	High IPV in Tac exposure beyond 6 mo after liver transplantation was not associated with imune-mediated graft injury
Dopazo *et al*[40], 2022	140	Deceased donor only	CV	High IPV between the third and sixth months appears to be an early and independent predictor of poorer liver transplant outcomes
Kim *et al*[41], 2022	636	Both living and deceased donor	CV	High Tac IPV was associated with increased risks of overall mortality and HCC recurrence in liver transplantation recipients with HCC

SD: Standard deviation; CV: Coefficient of variation; MLVI: Medication level variability index; DSA: Donor-specific antibodies; HCC: Hepatocellular carcinoma.

neurologic complications in patients with higher Tac CV. Most importantly, shortened graft and patient survival rates were also associated with Tac IPV[38]. Other authors investigated whether Tac CV, assessed between three to six months after LT, could be associated with worse graft and patient long-term outcomes[40]. In this study, lower long-term survival and poorer renal function were similarly observed in those subjects with high Tac CV. Another group of investigators also linked higher Tac IPV using CV with hepatocellular carcinoma (HCC) recurrence after LT[41]. Only one study up to now assessed the impact of Tac IPV after LT employing TTR[42]. The authors found that lower TTR in those subjects, irrespectively of Tac CV, was associated with a higher risk for *dn*DSA and long-term death-censored graft loss. The main findings related to LT are depicted in Table 3.

TAC IPV IN KIDNEY TRANSPLANTATION

Most of the studies published thus far demonstrated an adverse impact of Tac IPV on KT outcomes (Table 4)[43-68]. Most of them were performed in adult recipients using MLVI/SD[44], MAD[45-48,62,66], CV[49-60,63,64,67-68], TTR[61] or other methods[65]. In this regard, several authors have associated higher Tac IPV, usually measured more than 6 mo after KT, with BPAR[44-46], long-term graft loss or dysfunction[47-55,58,59,68] as well as with lower survival[50,51]. In some, but not all reports[62], higher Tac IPV was associated with the development of *dn*DSA[53,67], chronic active antibody mediated rejection[47] and chronic histological lesions in kidney grafts[54,56]. Most authors attributed those Tac IPV-related outcomes to non-adherence[43] and some[57-59] but not others[60] to genetic predisposition. Two other reports compared TTR[61] and a novel Tac variability score (TVS)[64] to conventional IPV measures and found that both were more reliable in their ability to predict worse outcomes after KT.

Concerning pediatric transplant recipients, Pollock-Barziv *et al*[26] were one of the first authors to show a significant association of higher Tac IPV and late graft rejection or loss. Similar findings were subsequently reported by other investigators who reported and association of higher Tac IPV with BPAR and graft loss beyond one year in children and adolescents submitted to KT[66-68].

Table 4 Tacrolimus intra-patient variability and kidney transplantation: Main findings

Kidney transplantation				
Ref.	**Sample size**	**Donor type**	**Tac-IPV assessment**	**Outcomes**
Borra *et al*[47], 2010	297	Both living and deceased donor	MAD	Significant relationship between high Tac-IPV and long-term graft failure
Ro *et al*[45], 2012	249	Both living and deceased donor	MAD	TAC IPV had a significant impact on rejection-free survival. The effect was influenced by CYP3A5 polymorphism
Sapir-Pichhadze *et al*[44], 2014	356	Both living and deceased donor	MLVI/SD	Increased time-dependent TAC SD may be an independent risk factor for adverse kidney transplant outcomes
O'Regan *et al*[49], 2016	394	Both living and deceased donor	CV	Inferior renal allograft survival was observed in recipients with higher Tac-IPV
Rodrigo *et al*[53], 2016	310	Deceased donor only	CV	Tacrolimus level variability is a strong risk factor for dnDSA development and death-censored graft loss
Whalen *et al*[46], 2017	376	Both living and deceased donor	MAD	Highly variable tacrolimus levels predict worse out- comes postrenal transplantation
Shuker *et al*[48], 2016	808	Both living and deceased donor	MAD	A high tacrolimus IPV is an independent risk factor for adverse kidney transplant outcomes that can be used as an easy monitoring tool to help identify high-risk RTRs
Vanhove *et al*[56], 2016	220	Both living and deceased donor	CV	High IPV is related to accelerated progression of chronic histologic lesions before any evidence of renal dysfunction
Rozen-Zvi *et al*[51], 2017	803	Both living and deceased donor	CV	The combination of high CV and exposure to low drug levels might identify high-risk patients in the early post-transplantation period
Goodall *et al*[50], 2017	688	Both living and deceased donor	CV	High tacrolimus IPV and clinic nonattendance are associated with inferior allograft survival
Sablik *et al*[62], 2018	248	Both living and deceased donor	MAD	A high Tac IPV per se does not predispose to the development of chronic active antibody mediated rejection (c-aABMR) but is associated with inferior graft survival once c-aABMR is diagnosed
Seibert *et al*[57], 2018	1472	Both living and deceased donor	CV	High variability of TAC dose increases risk of acute rejection. High variability of TAC trough increases risk of graft failure
Mo *et al*[54], 2019	671	Both living and deceased donor	CV	High IPV of Tac is associated with early deterioration of chronic histologic lesions as well as poorer long-term outcomes
Song *et al*[61], 2019	1241	Living donor only	TTR	Increasing the TTR of tacrolimus in the first year was associated with improved long-term outcomes in living kidney transplants, and TTR may be a novel valuable strategy to monitor tacrolimus exposure
Süsal *et al*[55], 2019	6638	Deceased donor only	CV	Even in patients with good outcome during the first 3 post-transplant years, a high IPV was associated with inferior graft survival, indicating that a fluctuating tacrolimus trough level at years 1, 2 and 3 post-transplant is a major problem in kidney transplantation
Rahamimov *et al*[52], 2019	878	Both living and deceased donor	CV	Monitoring CV can help detect the high-risk patients
Gold *et al*[66], 2020	1419	Deceased donor only	MAD	A more intense and less variable exposure to tacrolimus could improve graft survival strongly in patients with high TAC IPV
Stefanović *et al*[58], 2020	104	Both living and deceased donor	CV	Combined assessment of tacrolimus IPV and tacrolimus C0/D may categorize patients towards risk of graft deterioration in the long-term post-transplantation period
Stefanović *et al*[59], 2021	103	Both living and deceased donor	CV	Simultaneous assessment of Tac IPV, C0/D, and CYP3A5 genotype may identify patients at risk of deterioration of graft function in the long-term post-transplantation period
Kim *et al*[65], 2021	1080	Both living and deceased donor	CV	High tacrolimus IPV significantly increases the risk of graft failure and antibody mediated rejection in patients with high immunological risk
Park *et al*[63], 2021	1143	Both living and deceased donor	CV	TAC-IPV can significantly affect allograft outcomes even with a high mean TAC-C0
Yin *et al*[64], 2022	1343	Living donor only	CV	Tac variability score is a novel measure of Tac IPV with higher correlation with graft survival and more convenience in clinical use than CV after kidney transplantation
Baghai Arassi *et al*[67], 2022	48	Both living and deceased donor	CV	High Tac IPV is associated with an increased risk of dnDSA development and rejection episodes > year 1 posttransplant even in patients with low immunological risk profile

Nuchjumroon *et al* [60], 2022	188	Both living and deceased donor	CV	No evidence that the CYP3A5 polymorphisms significantly influence tacrolimus IPV during the 6 to 12 mo after kidney transplantation

SD: Standard deviation; CV: Coefficient of variation; MLVI: Medication level variability index; DSA: Donor-specific antibodies; TTR: Time in therapeutic range.

TAC IPV IN KIDNEY AND PANCREAS, AND BONE MARROW TRANSPLANTATION

Two studies have evaluated the impact of Tac IPV in the frequency of *dn*DSA, BPAR and graft loss in adult kidney and pancreas recipients[69,70] and in the occurrence of graft *vs* host disease after bone marrow transplantation[70]. The first report failed to disclose an association of Tac IPV with BPAR in adult recipients of kidney and pancreas transplants, but the main purpose of the study was to compare Tac IPV and graft function in groups of patients receiving two different Tac formulations[69]. Davis *et al*[38] on the other hand, demonstrated that Tac TTR was associated to a very high risk of *dn*DSA and a 4-fold risk of graft loss by five years, independently of Tac CV.

In respect to bone marrow transplant recipients, Marco *et al*[70] correlated high Tac IPV, measured by CV, with the occurrence of acute graft *vs* host disease in the first month after BMT (Table 5).

CONCLUSION

Altogether, available data up to now suggest that Tac IPV, possibly due to non-adherence and/or genetic, pharmacologic, or clinically significant factors, is associated with adverse outcomes after organ transplantation, particularly KT. The heterogeneity observed in the results obtained in the reports thus far are probably due to the retrospective design of most studies, the distinct methods used to assess Tac IPV, utilization of different immunosuppression protocols, distinct observation time frames and endpoints. Refinement or combination of different scores may improve usage of Tac IPV in clinical practice in the future.

Table 5 Tacrolimus intra-patient variability in pancreas and bone marrow transplantation: Main findings

Kidney and pancreas, and bone marrow transplant				
Ref.	**Sample size**	**Donor type**	**Tac-IPV Assessment**	**Outcome**
Torabi *et al* [69], 2020	39	Both living and deceased donor	CV	The once daily LCPT dosing may facilitate medication adherence and result in improved long-term outcomes
Marco *et al* [70], 2022	128	Living donor only	CV	Determination of Tac IPV soon after alloHSCT could be useful in identifying greater risks of aGVHD

CV: Coefficient of variation; LCPT: LCP-tacrolimus; alloHSCT: Allogeneic stem cell transplantation; aGVHD: Acute graft-vesus-host disease.

FOOTNOTES

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