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Effects of Tacrolimus Pharmacokinetic Variability on Acute Rejection and Long-Term Graft Function after Kidney Transplantation

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Abstract

Tacrolimus (TAC) is used for immunosuppression after kidney transplantation. Non-optimal TAC therapy contributes to renal toxicity, graft damage, and rejection. This paper reviews publications associating TAC intra-patient pharmacokinetic variability with long- and short-term transplant outcomes. The literature was reviewed performing systematic searches of MEDLINE and EMBASE databases from 1990 to May 2016 using appropriate Medical Subject Headings (MeSH) and key words. Titles and abstracts of hits were scanned for relevance, resulting in nine articles included in this analysis. Included articles were evaluated for content and relevance, and summarized. All studies were relatively small (N <400) non-randomized retrospective chart reviews. Only two articles did not show significant association between variability of TAC trough concentrations and at least one outcome after kidney transplantation. Four studies analyzing acute rejection (AR) showed significant association, while two did not. All studies analyzing graft loss or composite outcomes including graft loss showed significant association. Other studies showed association with donor-specific-antibody (DSA) development, but no association with renal function decline or overall patient survival. This review indicates an overall trend towards worse transplant outcomes in patients with higher TAC pharmacokinetic variability, however the size and design of the studies limit generalizability. Larger studies with more robust design are needed and should include genetic subgroup analysis and identification of sources of TAC variability to come to a definitive conclusion. Ideally, a dosing protocol incorporating wide varieties of genetic and clinical factors should be developed to optimize TAC dosing in transplant patients.

1 Introduction

Tacrolimus (TAC) has become the main calcineurin inhibitor used in immunosuppressive therapy after kidney transplantations, largely replacing cyclosporine in clinical use. (1) Despite its clinical benefits, TAC therapy is not without problems. TAC has a narrow therapeutic window and requires therapeutic drug monitoring of blood trough concentrations. Frequent dose adjustments are common in order to avoid nephrotoxicity associated with concentrations that are too high and, conversely, insufficient immunosuppression which has been shown to increase the risk of adverse outcomes such as acute rejection (AR) at sub-therapeutic concentrations.(2)

Outcomes and survival of kidney transplant patients have consistently improved over recent decades. Especially AR has become relatively rare and occurs in only less than 10% of recipients. Long-term graft function remains a problem, however, and approximately half of all kidney allografts are lost by 10 years after transplantation. (3) It is unclear what exactly causes this graft loss, but it is likely due to a variety of contributing factors and insufficient immunosuppression may play a large role.

TAC pharmacokinetics are influenced by genetic factors. Several single-nucleotide-polymorphisms (SNPs) are associated with altered TAC trough levels. (4) These SNPs contribute to inter-patient variability in TACs pharmacokinetics and partially determine initial starting doses, although there are other factors associated with intra-patient pharmacokinetic variability post-transplant including drug-drug interactions, food-drug interactions, changes in hepatic metabolism, and nonadherence. (5)

In recent years, intra-patient variability of TAC concentrations post-transplant has been investigated and proposed as a significant risk factor for long term complications such as late rejection, graft loss, donor-specific-antibody (DSA) development, and declining kidney function. Understanding the variables associated with intra-patient variability and strategies to reduce post-transplant pharmacokinetic variability may improve short- and long-term outcomes.

The long-term goal is to develop a comprehensive understanding of the influencing factors on TAC pharmacokinetics in renal transplant patients and their relationship to a recipients genetic make-up to optimize individual immunosuppressive therapy and enhance patient outcomes. Specifically, this paper aims to perform a systematic review of the literature related to the effects of TAC pharmacokinetic variability on short- and long-term outcomes after kidney transplantation. Databases were systematically searched for relevant publications, the literature was critically evaluated, and a summary of our findings is presented here.

2 Methods

2.1 Database Search

A review of the existing literature on TAC pharmacokinetic variability in kidney transplant patients and its association with short- and long-term outcomes was performed by systematically searching MEDLINE and EMBASE databases from 1990 to May 2016. Searches were performed using the following focused and auto-exploded Medical Subject Heading (MeSH) terms and key words: (1) exp *Tacrolimus/; (2) exp *Kidney Transplantation/; (3) variability.mp; and (4) variation.mp. Boolean operators were used to produce the final search algorithm: 1 AND 2 AND (3 OR 4). Results were limited to studies on human subjects and manuscripts in English language, which produced 171 hits in MEDLINE and 246 hits in EMBASE, for a total of 417 hits. EndNote Basic (Thomson Reuters, PA, USA) was used to store and organizes articles. After removal of duplicate hits using EndNotes Find Duplicate function as well as manual screening of titles and authors, 280 individual hits remained.

2.2 Inclusions and Reference Search

Each of the 280 hits was evaluated for inclusion by manually reading all titles and abstracts. Articles were included if the respective study or analysis attempted to relate a statistical measure of variability (standard deviation, intra-patient variability, or coefficient of variation) in TAC trough concentrations to objective short- and long-term outcomes after kidney transplantation. This method resulted in an inclusion of 8 articles. Furthermore, the reference sections of these articles were screened for additional relevant literature, resulting in the inclusion of 1 additional article, for a total of 9 articles used in our analysis.

2.3 Evaluation

Each included article was evaluated for several characteristics, including type of study design, timeframe during which TAC trough concentrations were measured post-transplant, number of subjects, specifics about patient populations (such as ethnicities and age ranges), statistical measure of TAC trough variability, types of measured outcomes, and primary results. Studies were also evaluated for their level of evidence using the Oxford 2011 Levels of Evidence grading scheme.

3 Results

3.1 Included Studies

The study selection process is summarized in figure 1. After removal of duplicate hits and manual screening of abstracts for relevance, eight full text articles plus one additional article pulled from their references were reviewed, for a total of nine articles included in our qualitative analysis. Each of those studies is summarized in table 1, listing year of publication, primary author, study design, level of evidence, number of included subjects, characteristics about the study population, type of statistical measure of variability used, time frame of measured TAC trough concentrations, outcomes assessed, and main findings.

3.2 Study Designs and Characteristics

Included studies were similar in design and strength of evidence. All studies were retrospective cohort analyses of transplant patients receiving TAC maintenance therapy. Studies were based on chart reviews focusing on the relationship between TAC pharmacokinetic variability and prognosis of outcomes after transplant. Applying the Oxford 2011 Levels of Evidence grading scheme, all studies displayed evidence of level 3 out of 5 (1 being the strongest and 5 being the weakest evidence).

All studies had relatively small sample sizes, ranging from 46 patients to 394 patients. None of the studies were multi-center trials, and study participants were relatively homogeneous within each study, representing local populations from the US, Canada, the Netherlands, Spain, Ireland, and Korea. Three of the nine studies focused only on pediatric patients, while the other six studies were limited to adult patients. Eight of the studies analyzed only kidney transplants, while one study of Canadian pediatric patients included kidney, lung, and liver transplants.

Pharmacokinetic variability in TAC trough concentrations among transplant patients was the main focus of all studies, however the time frames of included TAC levels varied greatly among studies: Five studies analyzed the variability of TAC trough concentrations within the first year after transplant, starting at 1, 3, 4, or 6 months after transplant. One study included all measurements between 1 month and 2 years after transplant. One study focused on later measurements between 1 year after transplant and last follow-up. Another study included all TAC trough concentrations within 1 year of study begin, at which point all included patients were at least 3 months post-transplant. Lastly, one study conducted two separate analyses, one of them including all TAC levels within 6 months prior to an acute rejection event, the other analyzing measurements between 6 months after transplant and last follow-up.

Each study used one of three statistical measures of variation to assess the degree of TAC pharmacokinetic variability among patients: Two studies used a simple standard deviation (SD), three studies used intra-patient variability (IPV), and four studies used a coefficient of variation (CV). There was no trend between the publication dates of articles and type of variability measures used or between the type of variability measure and its significance for outcomes. Each measure of variability differs slightly. Their definitions are given in equations 1 through 3.

3.3 Study Outcomes and Findings

The reviewed articles included a wide variety of outcome measures commonly seen in the progression of kidney transplant recipients. Most commonly, events of AR were the primary measured outcome, which was the case in six studies. Other analyzed outcomes were graft loss (two studies), DSA development (one study), kidney function decline (one study), overall survival (one study) or some form of composite including a variety of measures like AR, graft loss, kidney function decline, chronic nephropathy and glomerulopathy, or death (three studies). The majority of studies analyzed correlations with more than one outcome and only three of the studies focused solely on AR.

The majority of reviewed studies found a statistically significant correlation ($p < 0.05$) between higher levels of the respective measure of TAC pharmacokinetic variability and at least one negative outcome after transplantation. Only one study found no correlation with any outcome. Interestingly, of the six studies that

analyzed AR, four found a significant correlation with variability measures, while two did not. Furthermore, only the Korean study analyzed subgroups based on genotype. In this study, transplant recipients who expressed CYP3A5, an enzyme involved in the metabolism of TAC, showed an association between TAC IPV and AR, but patients that did not express CYP3A5 due to a polymorphism showed no association. All studies that analyzed graft loss or composite outcomes including graft loss demonstrated significant associations with TAC variability. Lastly, DSA development demonstrated association, while kidney function decline by itself and overall patient survival did not.

4 Discussion and Conclusion

While insufficient immunosuppression of transplant recipients is a known determinant of poor outcomes, only few studies have looked at the association between pharmacokinetic variability of immunosuppressive drug regimens and outcomes after kidney transplantation. A systematic review of the literature only found nine relevant studies published between 1990 and 2016 attempting to associate TAC variability with kidney transplant outcomes. Additionally, all of these studies were non-random retrospective chart reviews from highly specific populations and had relatively small sample sizes, the largest including 394 patients, limiting their generalizability.

Seven of the nine studies found some form of statistically significant association between TAC pharmacokinetic variability and negative transplant outcomes. Most importantly, all studies analyzing graft loss (two) or a composite outcome including graft loss (three) found significant association with TAC variability. Those that analyzed AR found mixed results, with four studies finding significant association and two finding no association. Additionally, one study found association with DSA development, while another study found no association with kidney function decline. The most recent study, which also had the largest sample size, found no association with overall patient survival, suggesting that high degrees of TAC variability may lead to adverse graft outcomes but not necessarily to the death of the patient if dialysis or re-transplant are available as rescue options. This systematic review shows that there may be an overall trend towards worse outcomes for kidney transplant patients demonstrating high levels of TAC pharmacokinetic variability, however the scarceness, retrospective designs, homogeneity, and small sizes of the reviewed studies limits the generalizability of this conclusion. All studies focused on TAC trough concentrations and did not assess variability in administered TAC doses, which could be a separate source of pharmacokinetic variability. Additionally, only one of the nine studies attempted subgroup analysis based on recipients genotype, and only included a single polymorphism.

In summary, larger studies with more robust designs are needed to draw definitive conclusions about the interaction of TAC pharmacokinetic variability and outcomes after kidney transplantation. Future studies should consist of larger prospective cohorts from multiple centers and populations and should streamline TAC measurement time frames as well as the statistic variability measure, preferably using the CV, as it is arguably the most robust of the three measures. (6) Additionally, future research should include analysis of genetics backgrounds of recipients, as several SNPs in TAC metabolizing enzymes have been identified and associated with TAC pharmacokinetics. (4, 7, 8) Lastly, attempts should be made to identify and measure definitive sources of TAC pharmacokinetic variability, such as non-adherence or drug-drug interactions. Ideally, a dosing equation or protocol should be developed incorporating a wide range of genetic and clinical factors to optimize TAC dosing.

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Tables

Year	Primary Author	Design	Evidence Level	N	Population	Var. Measure	TAC Measurement	Outcomes	Results
2010	Borra ⁹	Retro. Cohort	Level 3	297	Dutch Adults	IPV	6 – 12 mo. pt.	DCGF (graft loss, chronic allograft nephropathy, or doubling of sCr, > 12 mo. pt.)	High TAC IPV associated with more DCGF ($p = 0.003$)
2010	Pollock-BarZiv ¹⁰	Retro. Cohort	Level 3	144	Canadian Pediatrics (8 – 18 yo.); heart, kidney, lung, or liver transplants	SD	6 mo. prior to late rejection or last follow up 6 mo. pt. – last follow-up	Late AR (> 6 mo. pt.) Graft Loss (> 12 mo. pt.)	Higher TAC SD associated with more late rejection ($p = 0.02$) Increase in TAC SD > 2 associated with more graft loss ($p = 0.003$)
2011	Hsiau ⁶	Retro. Cohort	Level 3	46	US Pediatrics (2 – 22 yo.)	CV	1 – 12 mo. pt.	AR	High TAC CV associated with more AR ($p = 0.005$)
2012	Ro ¹¹	Retro. Cohort	Level 3	249	Korean Adults	IPV	6 – 12 mo. pt.	AR	High TAC IPV associated with more AR in CYP3A5 expressers ($p = 0.001$) but not in non-expressers
2012	Prytula ¹²	Retro. Cohort	Level 3	69	Dutch Pediatrics (3 – 18 yo.)	CV	0 – 12 mo. after study begin, at least 3 mo. pt.	eGFR Decline; Late AR (4 year follow-up)	No sig. association between TAC CV and eGFR decline ($p = 0.337$); High TAC CV associated with more late AR ($p = 0.045$)

2014	Sapir-Pichhadze ¹³	Retro. Cohort	Level 3	356	Canadian Adults	SD	12 mo. pt. – last follow-up	Composite Endpoint (late AR, transplant glomerulopathy, graft loss, death)	Increase in TAC SD associated with worse outcomes (p = 0.01)
2014	Schmid ¹⁴	Retro. Cohort	Level 3	81	Canadian Adults	CV	1 mo. – 2 years pt.	AR	No sig. association between TAC CV and AR (p = 0.65)
2015	Rodrigo ¹⁵	Retro. Cohort	Level 3	310	Spanish Adults	CV	4 – 12 mo. pt.	DCGL, dnDSA, AR	High TAC CV (> 30%) associated with more DCGL (p = 0.004) and dnDSA (p = 0.002), but not AR (p = 0.327)
2016	O'Regan ¹⁶	Retro. Cohort	Level 3	394	Irish Adults	IPV	3 – 12 mo. pt.	Graft Loss, Patient Survival (> 12 mo. pt.)	High IPV associated with more graft loss (p = 0.019), but not patient survival (p = 0.23)

Table 1. Summary of Reviewed Articles

TAC – Tacrolimus

CV – Coefficient of Variability

IPV – Intra-Individual Variability

SD – Standard Deviation

mo. – month

pt. – post transplant

yo. – years old

AR – Acute Rejection

DCGL – Death Censored Graft Loss

dnDSA – De Novo Donor Specific Antibodies

eGFR – Estimated Glomerular Filtration Rate

8 Figures

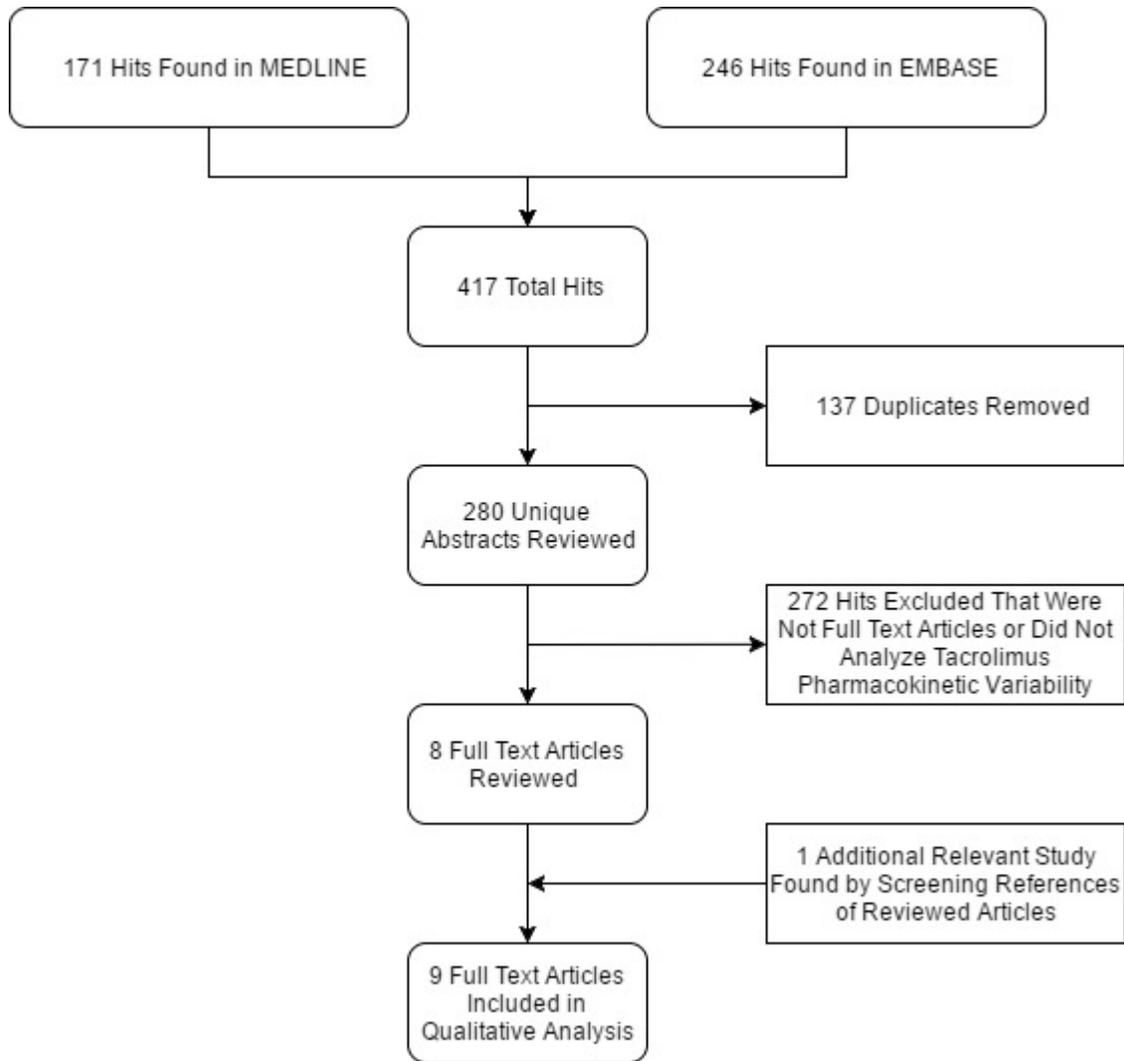


Figure 1: Study Section Flow Diagram

9 Equations

$$SD = \sqrt{\frac{1}{n} \sum_{i=1}^n (x_i - \bar{x})^2}$$

Equation 1. Standard Deviation

$$IPV = \frac{\frac{1}{n} \sum_{i=1}^n |x_i - \bar{x}|}{\bar{x}}$$

Equation 2. Intra-Patient Variability

$$CV = \frac{SD}{\bar{x}}$$

Equation 3. Coefficient of Variation