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Tacrolimus Therapeutic Response, Pharmacokinetics and Adherence in Liver Transplant Recipients

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Abstract

A high intra and interindividual pharmacokinetics variability characterize Tacrolimus. Data regarding factors influencing its pharmacokinetics and pharmacodynamics in liver transplantation are limited. This study aimed to assess tacrolimus therapeutic response, pharmacokinetics and adherence in liver transplant recipients. The study was conducted at the Clinical Pharmacology Department for 12 years, from January 2009 to March 2021. We included liver transplant patients treated with tacrolimus referred to our department for tacrolimus therapeutic drug monitoring. Secondly, we assessed tacrolimus adherence in liver

transplant recipients using a prospective Morisky questionnaire. We included 894 tacrolimus trough concentration C_0 from 76 patients. The mean age was 24.4 ± 10.2 years. The sex ratio M/F was 1.3. The median C_0 was 8.53 ± 4.7 ng/mL. In 48.2% of cases, the C_0 was in the therapeutic range. Children required higher weight doses of tacrolimus compared to adults. C_0 and C_0/dose ratios of tacrolimus were higher in adults and in male patients. Bilirubinemia, polypharmacy, and adherence were weakly correlated with C_0. Mycophenolate mofetil, prednisolone, mehylprednisolone, amphotericin B, fluconazole, and omeprazole were associated with increased tacrolimus C_0, while irbesartan was associated with decreased tacrolimus C_0. The intraindividual coefficient of variability (CV) ranged from 20.4 to 119%. The interindividual CV was 46.1%. The tacrolimus index of variability ranged from 1.6 to 15.1. Age greater than 18 years increased tacrolimus adherence by 3.892-fold in liver transplant patients. Tacrolimus bioavailability was higher in adults and men. Adherence increased by 3.892-fold in liver transplant adults.

Keywords

Tacrolimus; liver transplantation; transplant rejection; adverse drug reactions; pharmacokinetics; drug interactions; adherence

1. Introduction

Liver transplantation was first performed in adults in the US in 1963 [1]. The main indications in adults are currently hepatocellular carcinoma, viral C cirrhosis, and alcoholic cirrhosis [2].

Liver transplantation is associated with an overall survival rates of 88%, 80% and 75% at 1, 3 and 5 years, respectively [3]. Its overall mortality risk at one year is 79% lower than that in non-transplant patients [4].

Advances in immunosuppression and the development of new drugs were the main factors contributing to this improvement [3, 5].

Tacrolimus, a calcineurin inhibitor, remains the cornerstone of immunosuppressive therapy and one of the pillars of success in liver transplantation [6]. Tacrolimus involves inhibition of T lymphocyte activation and transcription of cytokine genes, including the interleukin-2 gene [7].

Calcineurin inhibitors are characterized by a narrow therapeutic index and significant intra- and inter-individual variability in their pharmacokinetics, which may be explained by major fluctuations in their bioavailability, essentially due to their variable metabolism by cytochrome P450 (CYP) 3A4/3A5 [8, 9].

This variability may lead to tacrolimus under-dosing, which can be associated with transplant rejection, or to an over-dosing, which can expose to a risk of toxicity and justifies tacrolimus therapeutic drug monitoring (TDM) in liver transplantation [10].

TDM is an essential approach in personalized medicine that helps clinicians to individualize tacrolimus therapy in order to optimize efficacy and reduce toxic adverse reactions [11].

However, data concerning factors influencing the pharmacokinetic variations of tacrolimus in liver transplant patients are limited.

We aimed to assess tacrolimus therapeutic response, pharmacokinetics and adherence in liver transplant recipients.

2. Methods

The first part of the study was retrospective. It was conducted in the Department of clinical pharmacology over 12 years (January 2009 to March 2021). In this part, we assessed therapeutic response, pharmacokinetics and influencing factors.

The second part of the study consisted in a prospective collection of liver transplant recipients' therapeutic adherence. This study was carried out using a Morisky questionnaire to consenting patients.

2.1 Data Collection

Patients' blood samples were collected with an information sheet completed by the attending physician. This form included information relating to:

- the patient: age, weight, department of origin, date of transplantation, associated pathology(ies), and date and time of sampling.
- biological data: creatinemia, glycaemia, kalaemia, bilirubinaemia, transaminases (aspartate amino transferase (ASAT), alanine amino transferase (ALAT)).
- the treatment: dosage, rythm of administration, treatment onset, date and time of last admisnistration of tacrolimus and associated drug(s). The liver transplantation immunosuppression protocol was based on a combination of corticosteroids and a calcineurin inhibitor (tacrolimus) then mycophenolate mofetil was associated with this dual therapy. Postoperatively, the liver transplant recipient received a treatment based on tacrolimus associated to mycophenolate mofetil 1 g orally twice a day, with a prescription of prednisone (20 mg/day) orally to be gradually reduced to stop it six months after liver transplantation in the absence of rejection [12].

2.1.1 Inclusion Criteria

We included liver transplant patients who were addressed for tacrolimus trough blood level at the steady state: Steady-state is generally reached after five half-lives of the drug in question. In our study, tacrolimus steady-state was assumed to be achieved after three days.

When informations were missing, patients were excluded (Patients with missing information such as age, tacrolimus brand name, or dosage were excluded from the study. Additionally, we excluded samples that either lacked a properly completed information form from the treating physician or were hemolyzed.)

2.1.2 Tacrolimus Pharmacokinetics

Tacrolimus pharmacokinetics was assessed using the following parameters:

* Tacrolimus trough blood level: Tacrolimus trough blood level expressed in ng/mL.
  The assay was carried out using chimiluminescent microparticle immuno-Assay technique [13].
  We considered tacrolimus trough blood level therapeutic range (TR) according to the liver transplantation phase:

- An early phase extending to 42 days following liver transplantation; during this phase, the TR of tacrolimus trough blood level is 10-15 ng/mL.
- A late phase extends beyond 42 days from the date of liver transplantation. In this case, the tacrolimus trough blood level TR is 5 to 10 ng/mL [14].

* Dw: the daily weight dose in mg/kg/day is defined as the ratio of the daily dose of tacrolimus divided by the body weight. The initial dose of tacrolimus recommended for liver transplantation is 0.10-0.20 mg/kg/day, taken in two separate doses in adults and 0.30 mg/kg/day in children [15].
* the ratio tacrolimus trough blood level/Dw: to reflect the bioavailability of tacrolimus.

2.1.3 Therapeutic Response

Therapeutic response consisted in an assessment of:

- Efficacy: Acute rejection is defined by its onset one to two weeks after liver transplantation. Under normal conditions of immunosuppressive treatments, acute rejection appears within four months' post-transplantation, with a peak during the first month. However, it can appear at any time if immunosuppressants are stopped. Chronic rejection is defined by its occurrence after many years and involves an immunological and non-immunological origin [16].
- and tolerance: Adverse drug events that were reported. As any immunosuppressive therapy, tacrolimus can induce numerous adverse effects, including mainly nephrotoxicity, neurotoxicity, metabolic disorders including diabetes and hyperlipemia, arterial hypertension, hypertrophic cardiomyopathy, gastrointestinal disorders, infections, tumors and malignant lymphatic processes [7].

2.1.4 Therapeutic Adherence

Adherence to treatment is defined as the behavior of patients who respect the recommendations of health professionals regarding taking medications, following the diet or modifying their lifestyle [17, 18]. Non- adherence is considered to be the most common cause of intraindividual variability in tacrolimus trough blood levels [19].

We conducted a prospective collection of adherence using the Morisky Medication Adherence Scale MMAS-8 questionnaire [20] that varies from 0 to 8. The thresholds are set as following:

A poor adherence corresponded to a score lower than 6.

An average adherence corresponded to scores 6 or 7.

A good adherence corresponded to a score of 8.

MMAS was only tested once per patient.

Parents provided the responses for children under 18 years old at the time of the MMAS questionnaire. However, for adults over 18, the patients gave the answers.

2.2 Statistical Analysis

2.2.1 Descriptive Study

Qualitative variables were expressed in terms of percentages. Quantitative variables were described in terms of means, standard deviations, and range (extreme values) or in terms of medians and interquartile ranges, depending on the characteristics of their distribution.

2.2.2 Analytical Study

We used parametric and non-parametric tests according to the distribution of the continuous data. Qualitative variables were compared using the Chi-squared test or Fisher's exact test. Quantitative variables were compared using the Student's T-test for independent samples or the Mann Whitney-Wilcoxon test.

Multivariate logistic analyses were performed to identify variables associated with adherence. Variables related to the studied event in the univariate analysis ($p < 0.2$) were included in the multivariate model. The p-significance threshold was set at 0.05 [21].

Statistical analysis was carried out using SPSS version 25.0 software.

2.3 Ethics Statement

The study was conducted according to Hilsenki's declaration and was approved by the local ethics committee of Charles Nicolle Hospital [22]. Written Informed Consent was obtained from the included patients.

3. Results

We included 894 samples of tacrolimus trough blood level providing from 76 liver transplant recipients (Figure 1).

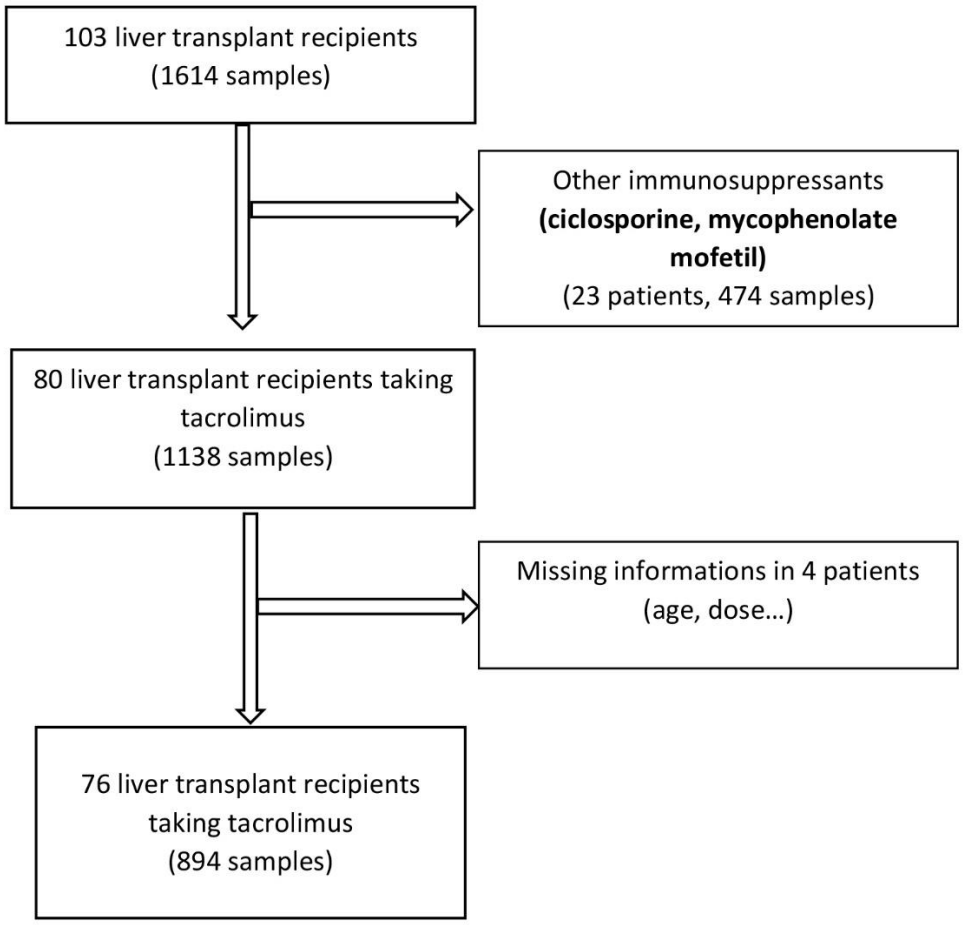

Figure 1 Flowchart of inclusion.

Among the patients, 33 were women, and 43 were men (respectively, to 365 and 529 samples). The women-to-men (W/M) gender ratio was 0.76.

The median age of patients was 25 (1 to 72), and the median age at the time of liver transplantation was 23 (1 to 68).

3.1 Tacrolimus Pharmacokinetics

Median tacrolimus trough blood level was 7.5 ng/mL (1.1-38.5 ng/mL), median dose was 4 mg/day (0.5-24 mg/day), median Dw was 0.1 mg/kg/day (0.01-0.63 mg/kg/day) and median tacrolimus trough blood level/Dw ratio was 74.3 (4.4-209). In 48.13% of cases, tacrolimus Dw was less than the recommended Dw, and in 14.41% of cases, it was higher than the recommended Dw.

3.1.1 Date of Transplantation

In our work, we found no significant difference between tacrolimus Dw (*p = 0.499*) and tacrolimus trough blood level (*p = 0.661*) according to the date of liver transplantation (7.4 ng/mL and 0.109 mg/kg/day in the early phase vs 7.5 ng/mL and 0.108 mg/kg/day in the chronic phase).

3.1.2 Gender Influence

Median tacrolimus trough blood level and the median ratio tacrolimus trough blood level/Dw were significantly higher in men. Men had significantly more supra-therapeutic tacrolimus trough blood levels (Table 1).

Table 1 Repartition of tacrolimus pharmacokinetic parameters according to gender.

	Men (n = 529, 59%)	**Women (n = 365, 41%)**	***p***
Tacrolimus trough blood levels:			
Median (ng/mL)	8 (1.1-38.5)	6.6 (1.1-30)	***0.000***
Subtherapeutic tacrolimus trough blood levels	123 (23%)	103 (28%)	
Tacrolimus trough blood levels in the therapeutic range	237 (45%)	194 (53%)	***0.000***
Supra-therapeutic tacrolimus trough blood levels	169 (32%)	68 (19%)	
Median weight dose (mg/kg/day)	0.113	0.10	*0.088*
Median tacrolimus trough blood level/daily weight dose	84	65.3	***0.02***

3.1.3 Age Influence

Adults had significantly higher tacrolimus trough blood levels and significantly lower Dw. The median tacrolimus trough blood level/Dw was significantly higher in adults, and they had significantly more supra-therapeutic tacrolimus trough blood levels (Table 2).

Table 2 Repartition of tacrolimus pharmacokinetic parameters according to age.

	<18 years (n = 344, 38.5%)	**≥18 years (n = 550, 61.5%)**	***p***
Tacrolimus trough blood levels:			
Median (ng/mL)	7 (1.1-24)	7.6 (1.1-38.5)	***0.001***
Subtherapeutic blood levels (n, %)	74 (21.5%)	152 (27.6%)	
Levels in the therapeutic range (n, %)	203 (59%)	228 (41.4%)	***0.000***
Supra-therapeutic levels (n, %)	67 (19.5%)	170 (**30%**)	
Median weight dose (mg/kg/day)	0.125	0.093	***0.000***
Median tacrolimus trough blood level/daily weight dose	54.15	97	***0.000***

3.1.4 Associated Drugs

That influenced tacrolimus trough blood levels are reported in Table 3.

Table 3 Associated drugs influencing tacrolimus trough blood levels.

Associated drugs	**Median tacrolimus trough blood levels (ng/mL)**		***p***
	With the associated drug	Without the associated drug	
Mycophenolate mofetil	7.95	6.9	***0.000***
Prednisolone	9.4	7.4	***0.002***
Prednisone	9	7.4	*0.06*
Methylprednisolone	10.1	7.4	***0.001***
Amphotéricine B	9.1	7.4	***0.013***
Fluconazole	15.5	7.4	***0.001***
Irbesartan	4.5	7.5	***0.009***
Omeprazol	10.75	7.4	***0.000***

3.2 Therapeutic Response

3.2.1 Transplant Rejection

Among the 76 patients, four had an acute transplant rejection (5.2%), and one had a chronic transplant rejection complicated by death (1.3%) (Table 4).

Table 4 Transplant rejection.

Patient	Age	Gender (W/M)	Mean tacrolimus trough blood levels (ng/mL)	Evolution
1	7	M	9.74	Acute rejection
2	19	F	4.02	Acute rejection
3	45	F	8.43	Acute rejection
4	48	F	7.41	Acute rejection
5	35	M	7.72	Chronic rejection and death

3.2.2 Adverse Drug Events

In our study, 26 patients (34.2%) experienced at least an adverse drug event (22.5% of the dosages performed) (Table 5).

Table 5 Adverse drug events repartition.

Adverse drug events		Patients (n, %)
Liver damage		12, 15%
Glycemic disorders	Diabetes	8, 10%
	Pre-diabetes	4, 5%
Renal failure		7, 9%
Digestive disorders		5, 7%
Neurological disorders	Tremor of the extremities	4, 5%
Cardiovascular disorders	Arterial hypertension	1, 1%
Hyperkaliemia		1, 1%

There were significantly more subtherapeutic tacrolimus trough blood levels in liver damage and renal failure (Table 6). In liver transplant recipients experiencing neurological disorders, there were significantly more supratherapeutic tacrolimus trough blood levels.

Table 6 Repartition of tacrolimus trough blood levels according to the therapeutic range in case of adverse drug events.

Tacrolimus trough blood levels (%)	Median trough blood level (ng/mL)	Subtherapeutic	In the therapeutic range	Supra-therapeutic	*p*
Liver damage	8.65	**19 (50%)**	12 (32%)	7 (18%)	***0.001***
Glycemic disorders	8.3	8	11	10	*0.526*
Renal failure	8.4	**23 (41%)**	15 (27%)	18 (32%)	***0.008***
Digestive disorders	7.3	5 (14%)	19 (51%)	13 (35%)	*0.194*
Neurological disorders	11.05	1	6	**8**	***0.04***
Hyperkalaemia	8.5	0	1	1	*0.767*

3.3 Therapeutic Adherence

Poor therapeutic adherence (score < 6) was reported in 11.5% of patients. Average therapeutic adherence (score 6 or 7) was noted in 50% of cases. Good therapeutic adherence (score = 8) was reported in 38.5% of patients.

According to the multivariate analysis, age greater than 18 years would increase the level of therapeutic adherence with tacrolimus 3.892 times in liver transplant recipients (Table 7).

Table 7 Age influence on therapeutic adherence.

	B	Wald	P	EXP B	Confidence Interval 95 EXP B
Age >18 ans	2.351	**3.892**	**0.049**	10.500	1.6-12.5

4. Discussion

To date, Tacrolimus remains the cornerstone of immunosuppressive therapy and one of the pillars of successful liver transplantation [6]. It is characterized by a narrow therapeutic index and significant intra- and inter-individual variability in its pharmacokinetics [8].

This variability may lead to tacrolimus under-dosing, which can be associated with transplant rejection, or to an over-dosing, which can expose to a risk of toxicity and justifies tacrolimus TDM in liver transplantation [23].

TDM is an important approach in personalized medicine that helps clinicians individualize tacrolimus therapy to optimize efficacy and reduce toxic adverse reactions [11].

However, data concerning factors influencing the pharmacokinetic variations of tacrolimus in liver transplant patients are limited.

This study aimed to assess tacrolimus therapeutic response, pharmacokinetics, patients' therapeutic adherence and influencing factors in liver transplant recipients.

4.1 Main Results

We conducted a retrospective study at the Clinical Pharmacology Department for 12 years to assess tacrolimus therapeutic response and pharmacokinetics, and, secondly, we administered a prospective Morisky questionnaire to assess therapeutic adherence in liver transplant recipients. The therapeutic response consisted of efficacy (transplant rejection) and tolerance (adverse events). Tacrolimus bioavailability was determined trough blood levels and doses. Seventy-six liver transplant recipients, corresponding to 894 samples, were addressed to measure their tacrolimus trough blood levels. The median age was 25 years. The gender ratio W/M was 0.76.

Median tacrolimus trough blood level was 7.5 ng/mL. This level was significantly higher in men (*p = 0.000*). Children required considerably higher doses of tacrolimus than adults and had lower tacrolimus trough blood levels and bioavailability of tacrolimus (*p = 0.001*). Transplant rejection was reported in 6.5% of liver transplant recipients. Adverse events were notified in 34.2% of patients. Median tacrolimus trough blood levels were significantly higher in patients with liver and neurological toxicity and if mycophenolate mofetil, prednisolone, methylprednisolone, amphotericin B, fluconazole, and omeprazole were associated. Irbesartan was associated with decreased tacrolimus trough blood levels.

38% of patients reported good therapeutic adherence. Age greater than 18 increased tacrolimus adherence by 3.892-fold in liver transplant patients.

4.2 Study Strengths

To our knowledge, this is the first multicenter study carried out on a national scale, bringing together liver transplant patients (76 patients and 894 tacrolimus trough blood levels' measurements), treated with tacrolimus, and coming from the public and private sectors of different specialties to assess the factors influencing tacrolimus pharmacokinetics, therapeutic response, and adherence in these liver transplant recipients.

Finally, this work highlights the value of interdisciplinary collaboration with the other departments involved in the overall care of liver transplant patients.

4.3 Study Limitations

In the retrospective study, some inadequacies were noted, notably missing or incomplete information while collecting data. This limited the number of patients included and the amount of data analyzed.

Furthermore, due to the polypharmacy of transplanted patients, the use of several immunosuppressive molecules, and other associated medications, it was difficult to incriminate tacrolimus directly in the genesis of certain adverse events, especially since the addressing services did not request a pharmacovigilance investigation.

4.4 Tacrolimus Pharmacokinetics

In our study, the mean tacrolimus trough blood level was 8.53 ng/mL, and the median was 7.5 ng/mL. The percentage of tacrolimus trough blood level in the TR was 48.2%.

Tacrolimus TDM is recommended in view of its narrow therapeutic index and the wide inter- and intra-individual variability in its pharmacokinetics. This is explained by major fluctuations in its bioavailability and metabolism by CYP P450 3A4/5. These factors make tacrolimus the target of numerous drug interactions [24, 25].

Recommendations for the dose and tacrolimus trough blood level vary between authors and the large pharmacokinetic variability makes it challenging to predict tacrolimus trough blood level that will be achieved with a well-defined dose. The TR considered in our department was 10-15 ng/mL during the first 42 days after transplantation and 5-10 ng/mL after that [14].

Brunet et al. recommended at a consensus conference that the tacrolimus trough blood level following liver transplantation should be between 10 and 15 ng/mL during the first three months following liver transplantation and between 5 and 10 ng/mL thereafter [26].

Regular blood-level monitoring of tacrolimus is necessary to personalize the dose for each patient and achieve optimal drug exposure [27].

There is no standard scheme for measuring tacrolimus trough blood level in liver transplant patients, and in our work, the number of determinations per patient varied.

The literature did not agree on the timescales for measuring tacrolimus through blood level [28]. The frequency of tacrolimus trough blood level measurements varied according to the time after liver transplantation and the patient's condition [29, 30].

4.4.1 Influence of Age

In our study, children required higher tacrolimus Dw than the pediatric population (median Dw for children was 0.125 vs. 0.093 mg/kg/day for adults). Our results are consistent with the literature.

McDiarmid et al. found that the oral dose of tacrolimus required to maintain similar tacrolimus trough blood levels was significantly higher in children than in adult patients ($p < 0.001$) during the first year of follow-up in a study of sixteen pediatric and 33 adult liver transplant patients treated long-term with tacrolimus. The mean Dw for the first year was 0.46 ± 0.4 mg/kg/day compared with 0.13 ± 0.01 mg/kg/day in adults [31].

Jain et al and Diarmid et al. also compared tacrolimus Dw in adult and pediatric liver transplant patients. Children required high doses of tacrolimus, up to five times the adult dose, to achieve the same tacrolimus through blood level. However, the recommended initial dose was comparable to that of adults, between 0.1 and 0.2 mg/kg/day in two doses, subsequently adjustable by TDM according to tacrolimus trough blood level [32].

In a study of 42 pediatric liver transplant patients during the first 14 days after liver transplantation, children under five years of age required a higher dose of tacrolimus compared to older children to achieve the same minimal tacrolimus trough blood level 0.12 (0.04-0.32) vs 0.09 mg/kg/12 h (0.01-0.18), the mechanism involved is not well elucidated. Nevertheless, age-related differences in drug elimination, such as CYP3A4/5 metabolism and P-gp transport, volume of distribution (Vd), protein and erythrocyte binding, or renal function, have been suggested [33].

The study by Durand et al, conducted in 179 children undergoing liver transplantation between 2002 and 2009, also showed that young children aged under five years required a higher daily dose of tacrolimus than older children to achieve the same tacrolimus trough blood level during the first few weeks of transplantation [34].

The study by MacFarlane et al. in 34 children and 111 adults with liver transplantation showed that the dosage was two to three times higher in children than in adults [35].

In this study, tacrolimus trough blood level was significantly higher in adults (7.6 vs. 7 ng/mL; $p = 0.001$). This result was inconsistent with the study by MacFarlane et al., which showed that tacrolimus trough blood levels in the pediatric population was not significantly different from Tacrolimus trough blood levels in adults during the 12 weeks post-transplant [35].

The literature has limited data concerning target tacrolimus trough blood levels in pediatric liver transplant patients [36].

In addition, the influence of age on pharmacokinetic parameters has been reported. In the study by Bruce et al., which included 172 adult liver transplant recipients aged between 18 and 66 years and measured tacrolimus trough blood level from 4 to 382 days post-transplant, no significant influence of age on tacrolimus free fraction, Vd or clearance was detected [37].

In a study of 68 liver transplant recipients who aged between 19 and 65, tacrolimus trough blood level was measured immediately after liver transplantation and several months or even years later, no significant effect of age on clearance or Vd was reported [37].

According to Fukatsu et al., tacrolimus trough blood level was determined during the first month after transplantation in 35 patients. Patients aged from 11 to 61 years were divided into two groups (<30 years, >30 years). The influence of age on clearance or Vd and free franction was not significant [37].

Tacrolimus bioavailability, reflected by the tacrolimus trough blood level/Dw ratio, was significantly higher in adults (54.15 vs. 97 in adults). Our result was consistent with the literature where a median tacrolimus trough blood level/Dw ratio of less than 51.83 was found in children, while a ratio greater than 51.83 was found in adult transplant recipients [38].

A lower tacrolimus bioavailability in young children may be related to the increased hepatic first pass of tacrolimus resulting from higher expression of CYP3A4 and CYP3A5 in the duodenum, which decreases with age. In addition, higher hepatic metabolism of tacrolimus has been observed in young children, leading to increased clearance and greater dose requirements for drugs metabolized by the liver. In addition, the higher intestinal expression of P-gp in young children may also contribute to these findings [34].

According to Thölking et al., the suggested explanation was that children required higher Dw than adult patients to achieve similar tacrolimus trough blood level. This could be explained by age-related differences in the maturation of tacrolimus pharmacokinetics, such as intestinal first-pass metabolism, volume of distribution, protein binding and/or hepatic metabolism and implies that younger children would be more susceptible to tacrolimus adverse effects [38].

4.4.2 Gender Influence

In our series, tacrolimus trough blood level was significantly higher in men than in women (8 vs. 6.6 ng/mL; p = 0.000), as was bioavailability (84 vs. 65.3; p = 0.02). However, in the literature, we did not find any specific studies comparing the doses and tacrolimus trough blood levels between the two genders in liver transplant recipients.

A comparison of tacrolimus blood levels in liver and kidney transplant patients found no significant statistical difference [30, 32].

In a study of 20 renal transplant recipients following the first oral dose, tacrolimus areas under the curve (0-12 hours) were lower, and half-lives were shorter in women. This may be due to a more significant metabolism of tacrolimus and a higher CYP3A4 and P-gp activity, as well as a 20-30% faster clearance of tacrolimus by CYP3A4 in women, which may explain the lower tacrolimus blood levels in women and their need for higher doses [39].

4.4.3 Influence of Post-Transplantation Delay

In our work, we found no significant difference between tacrolimus Dw and tacrolimus trough blood levels according to the date of liver transplantation (7.4 ng/mL and 0.109 mg/kg/day in the early phase vs. 7.5 ng/mL and 0.108 mg/kg/day in the chronic phase). The literature shows that they decreased significantly (11.27 ng/mL. to 8.4 ng/mL and 0.12 mg//kg/day to 0.1 mg/kg/day) after liver transplantation [40].

Several studies have reported a decrease in tacrolimus dose to maintain a similar tacrolimus trough blood level despite the post-transplant delay [21, 40, 41]. This may be due to a decrease in tacrolimus clearance and bioavailability.

The influence of time since liver transplantation on tacrolimus doses in children has not been well elucidated. A retrospective study of 21 pediatric liver transplant recipients showed that the mean daily dose achieving the same desired tacrolimus trough blood level during the first month after transplantation was significantly higher than that required 3.5 years later. However, other

studies found no change during the first year. In addition, two studies reported an increase in clearance with time after transplantation [37, 42].

Our study found no difference in tacrolimus trough blood level/Dw ratio according to the date of liver transplantation. Our results were in agreement with the study by Anaell et al. who did not find a statistically significant relationship between tacrolimus trough blood level/Dw and time post-transplant [43, 44]. According to Riva et al., tacrolimus trough blood level/Dw ratio increased with time post-transplant in children with liver transplantation [43]. This result was explained by decreased tacrolimus clearance due to drug interactions, increased bioavailability over time, or a combination of both factors [44].

4.4.4 Drug Interactions

This pharmacokinetic variability is due to either inhibition or enzymatic induction of CYP3A4 and P-gp [30].

In our study, we found that mycophenolate mofetil, prednisolone, methylprednisolone, amphotericin B, fluconazole, and omeprazole were associated with elevated tacrolimus trough blood levels. Irbesartan was associated with a decrease in tacrolimus trough blood level.

Tacrolimus is a substrate for the P-gp efflux pump. Drugs that are P-gp substrates may occupy the active sites of this pump, which could lead to higher absorption and bioavailability of tacrolimus. On the other hand, inhibition or induction of P-gp could lead to an increase or decrease in tacrolimus trough blood level [19, 45]. Tacrolimus is metabolized in the liver by cytochrome P450 (CYP), a substrate of CYP3A4 and CYP3A5 [46].

Inter- and intra-individual variability in tacrolimus pharmacokinetics is significant and may be partially explained by genetic polymorphism of the CYP3A genes [47]. Inhibitors of the CYP3A enzyme system may increase tacrolimus trough blood levels and increase the risk of toxic adverse events, while inducers may reduce tacrolimus trough blood levels and increase the risk of rejection [45].

In the literature, other factors influencing tacrolimus pharmacokinetics have been studied, including the ABCB1 transporter, hepatitis C profile, characteristics of the donor, race, albumin level, diurnal variations and circadian rhythm of tacrolimus exposure, anaemia and changes in protein levels, diet, jejunostomy and ascites [30, 37, 46].

4.5 Therapeutic Response

4.5.1 Transplant Rejection

Among the 76 patients, four had acute rejection (5.2%), one patient had chronic rejection complicated by death (1.3%), and one patient had chronic rejection complicated by death. Unfortunately, our study did not specify the timing of the occurrence of rejections.

According to the literature, the prevalence of rejection is reported in Table 8.

Table 8 Transplant rejection in liver transplant recipients.

Studies	Date	Patients	Type	Acute rejection	Chronic rejection	Delay after liver transplantation
Our study	2009-2020	76	Retrospective	5.2%	1%	Not precised
Lauren et al. 2015 [48]	2015	---	Review	50-100%	8%	Acute: 14 days chronic: 6-24 weeks
Choudhary et al. 2017 [49]	2007-2015	1437	Systematic review: 18 studies	24-80%	3-17% 2-9%	Variable according to the protocole (5-30 days)
Ali et al. [50]	2017	308	Retrospective, Egypt	20%	9.4%	-
Choudhary et al. [51]	2018	1232	Retrospective, India	-	1.9%	21 (8-44) months
Dogan et al. 2018 [52]	2002-2015	176 ≥18 years	Retrospective, Germany	20-40%	-	Median 2 months

Several studies reported that therapeutic regimens based on tacrolimus had a better survival rate than cyclosporine regimens [53] and that tacrolimus should be the first therapeutic choice after a liver transplantation [52-54].

4.5.2 Adverse Events

Among patients, 34% experienced adverse events consistent with literature data [37].

Liver Damage and Digestive Disorders. In our series, 15% of patients had liver damage, and their tacrolimus trough blood levels were significantly higher (8.65 vs 7.4 ng/mL; $p = 0.045$).

Most liver damage is induced by tacrolimus in the context of kidney transplantation [55]. In most studies, tacrolimus-induced liver injury is rare, most often cholestatic and less frequently cytolytic [55]. The prognosis for liver damage is generally reasonable. Cholestatic severe complications have been reported in a few studies [56]. The mechanism involved would be a reduction in bile flow or biliary secretion of glutathione, which is responsible for the detoxification caused by tacrolimus [30].

In our study, digestive disorders were reported in 7% of patients. Among these disorders, diarrhea was the most reported event. In the literature, the incidence of diarrhea in liver transplant patients treated with tacrolimus varied between 37% and 72% [57]. It has been suggested that diarrhea was due in part to effects on intestinal motilin receptors [57].
Our results are inconsistent with the literature data, which shows that diarrhea was associated with higher tacrolimus trough blood levels [58].

Diabetes and Prediabetes. In this study, 15% of patients developed a carbohydrate metabolism disorder. According to the literature, 16 to 70% of liver transplant recipients developed tacrolimus-induced carbohydrate metabolism disorder [32, 59, 60]. Tacrolimus seemed to be associated with a greater risk of induced diabetes mellitus than cyclosporine after liver transplantation [59, 61].

Various mechanisms are incriminated, including decreased insulin secretion, increased insulin resistance, and a direct toxic effect on the beta cell [62].

Renal Failure. Among patients, 9% developed renal failure. It is one of the most feared complications after organ transplantation and can occur in 14 to 60% of cases [5, 32, 63]. Tacrolimus produces afferent renal arteriolar vasoconstriction that may induce renal dysfunction and tubular injury. This effect is dose-dependent and reversible. However, it may be responsible for chronic kidney damage [5]. According to Lin et al., patients whose tacrolimus trough blood level was between 5 and 10 ng/mL during the first week after liver transplantation had significantly better renal function at 3 months post-transplant compared to patients who had a trough blood level between 10 and 15 ng/mL [63]. Thus, the authors recommended reducing the tacrolimus dose early after transplantation to prevent chronic renal effects [64].

Unlike our study, nephrotoxicity was associated with a higher tacrolimus trough blood level during maintenance treatment (8.2 versus 4.8 ng/mL, respectively) [36].

Neurological Disorders. Tremors of the extremities were reported in 5% of patients. In the literature, 10 to 28% of patients treated with tacrolimus develop neurotoxicity [65].

Median tacrolimus trough blood levels were significantly higher in patients with tremors (11.05 vs 7.4 ng/mL; $p = 0.04$). Our results were consistent with literature data [65].

According to the literature, tacrolimus levels above 15 ng/mL are associated with neurotoxicity [65], and tacrolimus blood levels of 5–8 ng/mL were associated with lower overall toxicity and neurotoxicity [66].

Hyperkalaemia. In our study, hyperkalaemia was reported in 1% of patients. In the literature, mild hyperkalemia frequently occurs during tacrolimus treatment, and it is not always modified by dosage adjustment [37, 58].

4.6 Therapeutic Adherence

38% of patients reported good therapeutic adherence. In the literature, the rate of non-adherence to immunosuppressive medications was 6.7% in liver transplant patients [67].

Over the past 20 years, various studies have reported rates of 20% to 50% nonadherence to immunosuppressive medications. In liver transplant patients, overall non-adherence rates of up to 15-40% have been reported, which is closely mirrored by the rates of no-shows for clinic appointments (3-47%) [68].

Therapeutic adherence is preferred to compliance and implies the patient's active participation in managing their illness and its treatments [69].

Adherence to immunosuppressive treatment involves taking medications and the correct treatment dose at the right time. Several approaches are currently used to estimate adherence to immunosuppressants [70].

In this study, age greater than 18 years increased tacrolimus adherence by 3.892-fold in liver transplant patients.

Several factors can influence treatment adherence; the World Health Organization has listed five dimensions that can interfere with adherence: factors related to the patients, the treatment, the socio-economic situation, the health system, and the disease [17].

Non-adherence with immunosuppressive treatment among solid organ transplant recipients constitutes a significant long-term problem with an unfavorable clinical and economic impact [71].

Poor adherence to immunosuppressive therapy can have negative consequences on long-term outcomes in transplant recipients. Therefore, improving treatment adherence is a crucial element for these patients.

5. Conclusions

Tacrolimus bioavailability was higher in adults and men. Some drugs, such as prednisolone, methylprednisolone, amphotericin B, fluconazole, and omeprazole, were associated with an elevated tacrolimus trough blood level. Irbesartan was associated with a decrease in tacrolimus trough blood level. Adherence increased by 3.892-fold in liver transplant adults.

Author Contributions

MD: Conceptualization, writing – original draft, formal analysis, writing – review and editing. KF: Software, Data analysis. RC: Conceptualization, Methodology, review and editing. MBS, SBH, EG, HE, AK, FM, RE: review. RD, ST: Supervising. All authors have read and approved the published version of the manuscript.

Competing Interests

The authors have declared that no competing interests exist.

Data Availability Statement

Data associated with a paper is available from the corresponding author upon reasonable request.

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