Original Research Article

Cyclosporine therapeutic window evaluation by Chebyshev's inequality method in kidney recipients

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ABSTRACT

Objective: The aim of this study was to identify a cyclosporine therapeutic range for kidney recipients.

Materials and methods: The cyclosporine exposure level was based on the calculation of the mean area under the concentration-time curve AUC(0–12). The AUC(0–12) was estimated using a Bayesian estimator and a 3-point limited sampling strategy. Cyclosporine exposure levels were obtained from 3 blood samples: 0, 1, and 3 h postdose; and analyses were performed using a liquid chromatography–tandem mass spectrometry method. The therapeutic window of cyclosporine was calculated by the Chebyshev’s inequality method with a 99% guarantee ($\alpha = 0.01$) using the IBM SPSS Statistics 20 software.

Results: It was found that the therapeutic window of cyclosporine estimated by the Chebyshev’s inequality method and put on the AUC(0–12) exposure lies in the ranges from 2.84–3.13 mg/h/L with the 99% confidence for the patients with the target AUC(0–12) exposure of 3.8 mg/h/L (posttransplantation time >1 year). The therapeutic window of cyclosporine differs in different posttransplantation time groups: the estimated AUC exposure range in the group of patients who have a graft longer than 5 years is 2.70–2.98 mg/h/L, and the estimated AUC exposure range in the group of patients who have a graft for 1–5 years is 3.05–3.75 mg/h/L.

Conclusions: Chebyshev’s inequality could be an appropriate and more precise method to determine the therapeutic window for cyclosporine in kidney recipients than the target AUC(0–12) value. Further studies should be conducted to evaluate patients with postoperative time <1 year.

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1. Introduction

Diabetes, hypertension, glomerulonephritis, cystic kidney and other disease may cause kidney failure. In 2011, it was more than 88,000 patients who were waiting for kidney transplants in the United States and 42,000 patients in Europe in 2012 [1,2].

The introduction of cyclosporine (CsA) in 1983 significantly improved the outcomes of all solid-organ transplants by reducing the risk of rejection [3].

Marked improvements in early graft survival and long-term graft function have made kidney transplantation a more life improving and cost-effective alternative to dialysis.

However, CsA bioavailability ranges from 20% to 50%, this drug involves numerous different interactions with other drugs and side effects (or toxicities) such as greater risks of cardiovascular disease [4,5], metabolic syndrome [6], bone loss, opportunistic and community-acquired infections, malignancies, and chronic kidney disease [7,8]. Moreover, cyclosporine usage in large doses and in long-term periods is particularly nephrotoxic [9–11].

Nevertheless, immunosuppression (IS) pharmacokinetics depends on the individual patient characteristics, disease anamnensis and unexplained immunosuppressants concentration fluctuations. Factors like drug-nutrient interactions, gender influence and polymorphism are responsible of blood drug concentrations variability. Drug monitoring is widely practiced for cyclosporine to assess a more required objective IS state that it can be used in clinical transplantation [12].

To determine drug prescribing trends not only treatment guidelines should be followed, but also population studies results should be taken into account. This means that knowing of the population ratio with drug leads to easier drug dosing and easier way to obtain exceptional cases. Therefore, continuous monitoring of population and evaluation of the results given by statistical methods are necessary.

Moreover, Ekberg et al. study showed difference between standard CsA dosing (target trough level of 150–300 ng/mL for the first 3 months and 100–200 ng/mL thereafter) versus low CsA dose (50–100 ng/mL). Study resulted that the standard CsA dosing group had a higher rate of infections, opportunistic infections and cytomegalovirus infections compared to the low CsA dosing group. Despite that further research should be applied [8].

In this study we tried to obtain the therapeutic window for patients receiving CsA in order to minimize cyclosporine dosing. The population pharmacokinetic model of cyclosporine was developed in kidney recipients. A three-point Bayesian estimator of AUC(0–12) was developed and is used to investigate the relation between cyclosporine pharmacokinetics in kidney recipients and determine if there is any indication to monitor this drug exposure in order to improve patient outcome based on individual AUC-controlled cyclosporine dosing and for identifying the therapeutic range of cyclosporine we tried a new Chebyshev’s inequality method model.

2. Materials and methods

2.1. Study object and selection of patients

192 patients, between 23 and 84 years, who underwent kidney transplantation and had a drug concentration monitoring of immunosuppressive agent cyclosporine in the university hospital during 2011, were included in the study. In total, there were 224 cases of cyclosporine monitoring.

2.2. Determination of AUC exposure

The cyclosporine exposure level was based on the calculation of the mean area under the concentration-time curve AUC(0–12). The AUC(0–12) was estimated using a Bayesian estimator and a 3-point limited sampling strategy [13]. The cyclosporine exposure levels were obtained from 3 blood samples: 0, 1, and 3 h post-dose, and the analyses were performed using a liquid chromatography- tandem mass spectrometry method. The first monitoring means the first evaluation of drug concentration in the blood in 2011.

2.3. Cyclosporine therapeutic window determination

Cyclosporine receiving patients had 4 AUC exposure targets: 6.0 mg h/L (<15 days), 5.5 mg h/L (15–60 days), 4.7 mg h/L (60 days–1 year), and 3.8 mg h/L (>1 year), which depended on the postoperative time. To evaluate the therapeutic window fitting, the analysis was performed in the groups with more than 15 patients (a statistically reliable model) and the therapeutic window for selected groups of the patients was estimated using Chebyshev’s inequality (a statistical probability theory).

2.4. Statistical calculations of cyclosporine AUC(0–12) exposure range

The therapeutic windows for cyclosporine receiving patients were estimated according to Chebyshev’s inequality theory and the AUC(0–12) exposures in the patients’ blood were obtained. To set the therapeutic range, the average cyclosporine blood level value of all the monitored patients was chosen as a starting point, Chebyshev’s inequality method was used to estimate the distances from the average cyclosporine blood level value on both sides, with a 99% probability that the other patients’ cyclosporine concentration will fall into the range that is obtained as distances from the average cyclosporine blood level value. For example, if the cyclosporine blood level, determined by the AUC exposure target, of the patients with the transplant age >1 year, is 3.8 mg h/L, the dispersion will be:

$$\alpha - 1 \mu = 3.8 \text{ mg/L} \alpha + 1$$

2.5. Statistical analysis

The data were processed using the IBM SPSS Statistics 20 software.
3. Results

3.1. Demographic data

The tested patients were coded and the only known demographic data were: date of birth, age, time after transplantation, monitoring date, and reason of monitoring (93 patients 48.4% had systemic monitoring, 58 patients 30.2% control of a dose adjustment, and 41 patients 21.4% unknown reasons).

3.2. Patients’ age

The mean patients’ age was 59.61 ± 0.98 years. The oldest patient was 84 years old, while the youngest patient’s age was 23. The study patients were divided into 4 groups: 20–34 years old, 35–49 years old, 50–64 years old, and >65 years old. The distribution of the patients by age groups is shown in Table 1.

3.3. Posttransplantation period

The average period after the transplantation was 3343.7 ± 168.98 days (9.16 years), while the minimum posttransplantation time for the monitored patients was 8 days and the maximum 9578 days (26.24 years). The study patients were also divided into 5 groups according to the transplant time. The posttransplant time distribution is shown in Table 2.

3.4. The survey sample

The calculations were performed only for 2 groups of the patients: patients with the transplant time 1–5 years and patients with the transplant time >5 years (in total, 177 patients, and 92.2%). The AUC exposure target for both groups was the same, i.e., 3.8 mg h/L. The groups of the patients with the transplant time <15 days (2 patients, 1.0%), 15–60 days (2 patients, 1.0%), and 60 days–1 year (11 patients, 5.8%) were excluded from the calculations due to a small number of patients within the group and a statistically unreliable model. Another 2 patients were excluded due to the AUC calculation error (2 patients, 0.6%).

3.5. Estimation of cyclosporine therapeutic window

The first cyclosporine monitoring was made for 175 patients including the patients receiving cyclosporine monotherapy and the patients receiving 2 drugs: cyclosporine + mycophenolate mofetil (1 patient was receiving CsA + Everolimus). The AUC exposure target was 3.8 mg h/L for all the monitored patients. The cyclosporine therapeutic window was estimated using Chebyshev’s inequality in all group; according to this theory, it was found that the AUC0–12 exposure ranged from 2.84 to 3.13 mg h/L with a 99% confidence (the average AUC0–12 exposure was 2.99 ± 0.056 mg h/L, maximum 5.43 mg h/L, and minimum 1.39 mg h/L) (see Fig. 1). Chebyshev’s inequality guarantees that in any data sample or probability distribution, “nearly all values are close to the mean” [14].

Later patients’ blood samples were divided in two groups: the first group with the transplant time 1–5 years, and the second group >5 years. Despite the fact that the AUC exposure target is the same (3.8 mg h/L) in the groups of the patients with a different posttransplantation time, cyclosporine therapeutic window was evaluated for both groups. We found it different in different posttransplantation time groups: the estimated AUC exposure range was 2.70–2.98 mg h/L (the average AUC0–12) exposure was 2.84 ± 0.054 mg h/L, maximum 4.38 mg h/L, and minimum 1.39 mg h/L in the group of the patients who had a graft longer than 5 years, and 3.05–3.75 mg h/L (the average AUC0–12 exposure was

<table>
<thead>
<tr>
<th>Table 1 – Distribution of patients by age groups.</th>
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<td>Age group</td>
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<tr>
<td>20–34</td>
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<tr>
<td>35–49</td>
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<tr>
<td>50–64</td>
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<td>&gt;65</td>
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<tr>
<td>Total</td>
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<table>
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<tr>
<th>Table 2 – Distribution of patients by posttransplantation time.</th>
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<tbody>
<tr>
<td>Posttransplantation time</td>
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<tr>
<td>--------------------------</td>
</tr>
<tr>
<td>&lt;15 days</td>
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<tr>
<td>15–60 days</td>
</tr>
<tr>
<td>60 days–1 year</td>
</tr>
<tr>
<td>1–5 years</td>
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<tr>
<td>&gt;5 years</td>
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<tr>
<td>Total</td>
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</table>

Fig. 1 – Histogram of cyclosporine AUC exposure range in patients receiving CsA after the first monitoring than target AUC exposure is 3.8 mg h/L. X-axis shows patients’ AUC values in h mg/L and y-axis demonstrates the frequency of the patients. This histogram demonstrates that defined cyclosporine target (3.8 h mg/L) does not match the bigger part of population who has a lower cyclosporine blood level.
3.60 ± 0.13 mg h/L, maximum 5.43 mg h/L, and minimum 1.65 mg h/L) in the group of the patients who had a graft for 1–5 years.

3.6. Therapeutic window fitting

After Chebyshev’s inequality was used to estimate the cyclosporine therapeutic window using the blood samples of 175 patients, the calculated therapeutic window fitting was evaluated. It was found that there were 29 patients (16.6%) within the estimated therapeutic range (2.84–3.13 h mg/L); 79 patients (45.1%) had a lower AUC exposure than the estimated therapeutic window and 67 patients (38.3%) had a higher AUC exposure. To ensure that the patient maintains a concentration of drug within his/her system that is within the estimated therapeutic range, the second monitoring was performed for 16 patients (9.1% of the total number of patients). Of those who underwent the second monitoring, 6 patients (37.5%) had a lower AUC exposure than the estimated range, 8 patients (50.0%) had a higher AUC exposure, and there were 2 patients (12.5%) whose AUC exposure was in the estimated range. The data are shown in Table 3. The third monitoring was performed in 2 patients, neither of which was within the therapeutic range (2.85–3.14 h mg/L); and one of these 2 patients had the fourth monitoring.

After the patients were grouped according to their posttransplantation time, we also evaluated the therapeutic window, depending on the posttransplantation time, fitting in 2 different posttransplantation time groups. It was found that in the >5-year posttransplantation time group, there were 28 patients (21.7%) within the estimated therapeutic range (2.70–2.98 h mg/L) and in the 1–5-year posttransplantation time group, there were 17 patients (37.0%) within the estimated therapeutic range (3.05–3.75 h mg/L). Further therapeutic window fitting data is provided in Table 4.

The study results showed that the cyclosporine therapeutic window, calculated according to the posttransplantation time, better defines the dosage accuracy in comparison with the cyclosporine therapeutic window, calculated for both study patient groups together (1–5-year and >5-year posttransplantation time groups together). Both compared groups had the same AUC exposure target of 3.8 mg h/L. The study data confirmed that 17 patients (37.0%) were within the estimated therapeutic window in the 1–5-year posttransplantation time group and 28 patients (21.7%) were within the estimated therapeutic window in the >5-year posttransplantation time group vs. 29 patients (16.6%) in all the study group of 175 patients.

4. Discussion

The drug blood concentration is a variable, quantitative, and continuous value. We accept that patients’ cyclosporine concentrations in the blood are numerical characteristics of continuous random variables, and we can calculate the mean and the dispersion for random variables. To analyze the mean and the dispersion of the numerical characteristics of continuous random variables, \( \chi^2 \), Fisher’s, and Student’s distributions can be used.

Student’s t distribution and Snedecor–Fisher’s F distribution are used in statistical tests. The first one is frequently used to estimate the mean \( \mu \) of a normal distribution when the variance \( \sigma^2 \) is not known, which a common situation is. The second is a special purpose distribution used to estimate the ratio of the variances of 2 normal distributions [15,16].

In the probability theory and statistics, the chi-squared distribution (also Chi-square or \( \chi^2 \)-distribution) with \( k \) degrees of freedom is the distribution of a sum of the squares of \( k \) independent standard normal random variables. It is one of the most widely used probability distributions in inferential statistics, e.g., in hypothesis testing or in construction of confidence intervals [17–20].

However, the limit laws (1. law of large numbers, 2. the central limit theorem, and 3. Chebyshev’s inequality) exist in the mathematical theory. They are used to calculate the limit of a function. The AUC could be one of the examples of the limit of a function. We used the Limit Laws to determine the function interval by measuring the area under the concentration–time curve. The drug concentration in the blood over time is approaching 0, i.e., \( \Delta c \to 0 \) and \( t \to \infty \); so this is the ultimate variable, which can be used in Chebyshev’s inequality (Fig. 2).

“In probability theory, Chebyshev’s inequality (also spelled as Tchebyshoff’s inequality) guarantees that in any data sample or probability distribution, “nearly all” values are close to the mean – the precise statement being that no more than \( 1/k^2 \) of the distribution’s values can be more than \( k \) standard deviations away from the mean. The inequality has great

<table>
<thead>
<tr>
<th>Posttransplantation time</th>
<th>CsA concentration (h mg/L)</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1–5 years</td>
<td>&gt;3.04</td>
<td>19</td>
<td>41.3</td>
</tr>
<tr>
<td></td>
<td>3.05–3.75</td>
<td>17</td>
<td>37.0</td>
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<td></td>
<td>&gt;3.76</td>
<td>10</td>
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<td></td>
<td>Total</td>
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<td>100.0</td>
</tr>
<tr>
<td>&gt;5 years</td>
<td>&lt;2.69</td>
<td>51</td>
<td>39.5</td>
</tr>
<tr>
<td></td>
<td>2.70–2.98</td>
<td>28</td>
<td>21.7</td>
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<td></td>
<td>&gt;2.99</td>
<td>50</td>
<td>38.8</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>129</td>
<td>100.0</td>
</tr>
</tbody>
</table>

Table 4 – The therapeutic range accuracy between transplantation time groups.
utility because it can be applied to completely arbitrary distributions (unknown except for mean and variance)”.

“Let \(X\) be a random variable with an expected value \(\mu\) and a finite variance \(\sigma^2\). Then for any real number \(k > 0\),

\[
Pr(|X - \mu| \geq k\sigma) \leq \frac{1}{k^2}
\]

“Only the cases \(k > 1\) provide useful information”. This can be equivalently stated as

\[
Pr(|X - \mu| \geq \sigma) \leq \frac{\sigma}{\sigma^2}.
\]

As an example, using \(k = \sqrt{2}\) shows that at least half of the values lie in the interval \((\mu - \sqrt{2}\sigma, \mu + \sqrt{2}\sigma)\) [14].

Chebyshev’s inequality can be used for the selected desired random variable and can be used to calculate the dispersion (spread) from the selected variable with the selected probability interval.

Accurate cyclosporine (CsA) dosage monitoring is still a problem because the right dose selection for the patients provides an effective and safe therapy and improves clinical outcomes. The only way to calculate an appropriate CsA dose for the patients is drug blood plasma concentration monitoring, the so-called therapeutic drug monitoring (TDM).

TDM could be performed by monitoring a complete pharmacokinetic profile and blood sampling from 0 to 12 h after CsA dosing or monitoring the limited amount of samples (2, 3, or more) within a 12-h period after a drug intake. For almost 25 years, the CsA therapy has been monitored through blood levels (\(C_0\)). \(C_0\) levels were kept within the therapeutic range, with target levels in various transplantation centers (in the United States, often 150–250 \(\mu g/L\); in Europe, 100–200 \(\mu g/L\)), but a significant number of patients experienced a lack of efficacy or renal toxicity [21]. Blood level monitoring (\(C_0\)) does not provide the best exposure index; it is a weak predictor of acute rejection or toxicity in renal [22] or liver [23] transplant patients.

The measuring of CsA through blood plasma concentration was replaced by the measurement of the AUC. The AUC calculated from the individual pharmacokinetic profile has more information on drug exposure and it is a better predictor of a clinical outcome. It is very difficult to apply the AUC estimation from a complete 12-h pharmacokinetic profile in the day-to-day outpatient follow-up; the possibility to calculate the AUC within the reasonable percent of error using only a few samples is more convenient for the patient and physician as well. Thus, due to that in recent years most of the studies have been based on various minimization strategies with an aim to reduce maintenance immunosuppressive drug exposure in renal transplant recipients. In these studies, 2- or 3-point pharmacokinetic sampling was used, and these minimization strategies were focused on calcineurin inhibitors (CNIs) [24–28].

The prediction of the CsA AUC using a limited sampling method in patients was for the first time introduced by Foradori and coworkers, who found a very high correlation \((r = 0.910)\) between the measured and the predicted AUC within 3 sampling points at 1, 2.5, and 5 h after dosing [29]. Different time points were proposed by various investigators for the 3-point sampling strategy, i.e., 0, 1, and 2 h or 0, 1, and 3 h or already mentioned 1, 2.5, and 5 h, but the error in the AUC prediction using the strategy of 3 very early sampling points after a CsA intake is identical to that obtained at 1.5, 8, and 11 h.

In 1995, it was shown that \(C_0\) levels correlated poorly with the systemic CsA exposure as measured by the area under the 12-h concentration versus time curve AUC\(_{0-12}\) because of extensive interpatient and intrapatient variability in CsA absorption and metabolism [30]. A number of patients are overexposed or underexposed to the drug when \(C_0\) monitoring is used. The studies showed that achievement of AUC (0–4) values of 4400–5500 \(\mu g/L\) or C2 levels of 1500–2000 \(\mu g/L\) during the first 3 days after transplantation minimizes the risk of rejection and improves the graft function [31,32]. However, in comparison with \(C_0\) levels, the single-point \(C_2\) level does not correlate better with the total systemic exposure of CsA as measured by the AUC\(_{0-12}\) [33]. \(C_2\) monitoring, thus, prevents underexposure and provides higher efficacy, but does not give better protection than \(C_0\) monitoring against overexposure of the drug with the risk of long-term nephrotoxicity.

As compared with \(C_0\) monitoring, the use of the limited sampling strategy model has improved the estimation of systemic exposure, but equations are rigid and not reliable in patients with an abnormal absorption profile. A compartmental population pharmacokinetic model for CsA in renal transplant recipients combined with the maximum a posteriori Bayesian fitting method seems more practical because it offers an important advantage of flexibility in sampling times after drug administration and provides the opportunity for long-term AUC-guided dosing [33]. The performance of this model is comparable to that of the limited sampling strategy model in kidney transplant patients and superior in simultaneous pancreas and kidney recipients.

A simplified strategy with 3 time points of blood collection could be applied for the monitoring of the cyclosporine exposure in monotherapy with CsA and in combination with other immunosuppressive medications as well. The limited strategy of 3-point sampling taken early after dosing (at 0, 1, and 3 h) allows an excellent and perfectly reliable prediction of the actual AUC. The data from previous studies showed that the best results were obtained with a 3-point strategy (0, 1, and 3 h after Neoral dosing; error in prediction –9.0 to 7.2%), which gave an excellent correlation between measured and predicted AUC \((r = 0.989)\) [34].
In combination therapy of CsA and mycophenolate mofetil (MMF), a simplified strategy with 3 time points of blood collection at 0, 1, and 3 h after the combination of CsA and MMF allowed adequate and accurate prediction of the daily exposure to CsA. The AUC prediction with 2-point sampling at 2 and 6 h was not as good with a very large error in prediction (only 59% of the estimated AUC were within the accepted range). This limitation was even more evident when the 0- and 2-h time points were examined, in which only 51% of the AUC estimates were included in the accepted range of variation (−10 to 10%).

In the application of a 3-point strategy (0, 1, and 3 h after CsA-MMF dosing), the regression analysis documented a highly significant \( (P < 0.001) \) correlation between the measured and the predicted AUC \( (r = 0.980) \). The correlation analysis using a 2-point (2 and 6 h) equation for predicting the AUC gave more dispersed values around the line of identity, despite a still significant regression value \( (r = 0.926, P < 0.001) \), as compared with the full AUC. Similarly, the 2-point strategy with sampling at 0 and 2 h post-CsA-MMF dosing provided a highly significant correlation between the measured and the predicted AUC \( (r = 0.890, P < 0.001) \).

For a steady state dose, pharmacokinetics data one month after transplantation, the 3-point strategy of the AUC using the multiple linear regression analyses model showed the best prediction. The correlations of the single-point blood level were lower than those of the corresponding sampling time in the 2-point strategy. The 3-point combinations, \( C_2 + C_4 + C_{12} \), showed the best prediction \( (r^2 = 0.982; P < 0.001) \) in comparison with the 2-point combination, \( C_2 + C_{12} \) \( (r^2 = 0.937; P < 0.001) \) [35,36].

The limited sampling strategy model (the Bayesian estimator and the 3-point limited sampling strategy used to calculate the mean area under the concentration–time curve \( \text{AUC}_{0–12} \) of the cyclosporine exposure) used in our study is suitable not only for kidney transplants, but for almost all solid organ transplants using cyclosporine. The limited sampling strategy model was selected to predict the full 12-h CsA AUC in allogenic hematopoietic stem cell transplant patients receiving CsA. And as a recent study has shown, the major findings are that the concentration measurements, at \( C_2 \) and \( C_4 \) time points, correlated best with \( \text{AUC}_{0–12} \) after an oral administration of CsA in allogenic stem cell transplant patients rather than through blood level. These time points provide a more accurate measure of post-transplant immunosuppression. Moreover, this study also showed that the more points are measured, the better correlation results we get. That is why we used 3 points instead of using 1 measurement point (through level) [37].

These data suggest that there could be a therapeutic window for individual dosing that combines maximum efficacy with minimal toxicity. The \( \text{AUC}_{0–12} \) exposure of cyclosporine of the studied population using the Chebyshev’s inequality method calculations demonstrated that the cyclosporine therapeutic window, calculated according to the post-transplantation time, better defines the dosage accuracy in comparison with the cyclosporine exposure, calculated according to the target AUC value. Moreover, it was noticed that none of these therapeutic ranges reached the CsA \( \text{AUC}_{0–12} \) monitoring target (3.8 mg/h/l). These results could be of benefit for various ongoing minimization strategy studies with an aim to reduce maintenance immunosuppressive drug exposure in renal transplant recipients [24–28].

Measuring CsA concentrations at the time points 0, 2, and 3 h postdose provides an excellent estimation of the \( \text{AUC}_{0–12} \). However, it remains to be shown that therapeutic drug monitoring of CsA based on the AUC estimation will provide protection against long-term CsA nephrotoxicity [15].

5. Conclusions

The study data demonstrates that Chebyshev’s inequality method could be an appropriate method to determine the cyclosporine therapeutic window in order to select an optimal dosing regimen and further studies should be conducted to evaluate patients with postoperative time <1 year.

Conflict of interest

The authors state no conflict of interest.

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