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Optimising therapy with cyclosporine at the University Medical Centre Maribor

Optimizacija zdravljenja s ciklosporinom v Univerzitetnem kliničnem centru Maribor

Mateja Stopinšek,[1] Polonca Drofenik,[1] Sebastjan Bevc,[2,3] Zlatko Roškar,[4] Iztok Holc,[5] Maksimiljan Gorenjak,[6] Aleš Mrhar[7]

[1] Central Pharmacy, University Medical Centre Maribor, Maribor, Slovenia
[2] Department of Nephrology, Division of Internal Medicine, University Medical Centre Maribor, Maribor, Slovenia
3 Faculty of Medicine, University of Maribor, Maribor, Slovenia
4 Department of Haematology and Hematologic Oncology, Division of Internal Medicine, University Medical Centre Maribor, Maribor, Slovenia
5 Department of Rheumatology, Division of Internal Medicine, University Medical Centre Maribor, Maribor, Slovenia
6 Department of Laboratory diagnostics, University Medical Centre Maribor, Maribor, Slovenia
7 Faculty of Pharmacy, University of Ljubljana, Ljubljana, Slovenia

Correspondence/ Korespondenca:
Mateja Stopinšek, e: mateja.stopinsek@gmail.com

Abstract

Background: Cyclosporine is an immunosuppressive drug used in transplantations and autoimmune diseases. It is a drug with a narrow therapeutic index, numerous interactions and high inter- and intraindividual variability. Therefore, therapeutic drug monitoring (TDM) and individual dosing can contribute greatly to the safety and efficacy of cyclosporine treatment. The aim of our study was to assess the importance of computerised TDM service within clinical pharmacy in the optimization of cyclosporine treatment in patients with autoimmune diseases.

Methods: In 2016, we conducted a 6-month prospective study, which involved all patients on permanent cyclosporine therapy who were treated at the UMC Maribor due to autoimmune diseases. Our study was divided into two periods. i.e. the observation and the intervention period, in which the use of pharmacokinetic software DoseMe® was introduced to interpret cyclosporine blood concentration measurements and to calculate the appropriate dosing regimen. There were 8 patients included in the observation period and 9 patients in the intervention period, 6 patients were monitored during both periods. By monitoring the selected parameters, the efficiency of cyclosporine treatment during both periods was compared. We used the IBM SPSS Statistics® and Microsoft® Office Excel for statistical analysis.

Results: 24 measurements of cyclosporine minimum concentration (C_0) were carried out in the observation period and 18 measurements during the intervention period. The response time required for a measured concentration to be interpreted and recorded in the patient's medical record was 17.4 days during the observation period and 6.8 days during the intervention period. In both periods, one-fifth of the measured concentrations were not interpreted in patients' medical records by physicians. The percentage of cyclosporine concentration measurements that were within the therapeutic range increased from 38% to 67% during the intervention period. The number of days when patients' blood levels of cyclosporine were within the therapeutic range increased from 37.5 to 70 days.

Conclusion: In this study, the importance of therapeutic drug monitoring to optimize cyclosporine treatment was confirmed. During the intervention period, the response time, the number of concentration measurements within the therapeutic range and the number of days when patients' cyclosporine blood levels were within the therapeutic range were improved. In our set of patients, DoseMe® software was found to be a useful tool for optimizing cyclosporine treatment.

Izvleček

Izhodišče: Ciklosporin je imunosupresivna zdravilna učinkovina, ki se uporablja pri presaditvah čvrstih organov in krvotvornih matičnih celic ter pri zdravljenju nekaterih avtoimunskih bolezni.

Key words:
therapeutic drug monitoring; cyclosporine; autoimmune diseases; individual dosing; pharmacokinetic program

Ključne besede:
terapevtsko spremljanje koncentracij; ciklosporin; avtoimunske bolezni; individualno odmerjanje; farmakokinetični program

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Ker gre za učinkovino z ozkim terapevtskim območjem, številnimi interakcijami ter veliko inter- in intraindividualno variabilnostjo farmakokinetičnih parametrov, lahko s terapevtskim spremljanjem koncentracije v krvi (*angl.* Therapeutic Drug Monitoring, TDM) in z individualnim odmerjanjem bistveno izboljšamo varnost ter učinkovitost zdravljenja. V raziskavi smo želeli preveriti, ali računalniško podprta storitev TDM kot dejavnost klinične farmacije prispeva k optimizaciji zdravljenja s ciklosporinom pri bolnikih z avtoimunskimi boleznimi.

Metode: V UKC Maribor smo leta 2016 izvedli prospektivno 6-mesečno raziskavo, v katero smo vključili vse bolnike, ki se trajno zdravijo s ciklosporinom zaradi avtoimunskih bolezni. Raziskava je bila razdeljena na opazovalno in na intervencijsko obdobje, v katerem smo za interpretacijo izmerjenih koncentracij ciklosporina v krvi ter za izračun najprimernejšega režima odmerjanja uvedli farmakokinetični program DoseMe®. V opazovalnem obdobju je bilo v raziskavo vključenih 8, v intervencijskem pa 9 bolnikov; od tega smo 6 bolnikov spremljali v obeh obdobjih. S spremljanjem izbranih parametrov smo primerjali uspešnost zdravljenja s ciklosporinom v obeh obdobjih. Za statistično analizo rezultatov smo uporabili računalniška programa IBM SPSS Statistics® in Microsoft® Office Excel.

Rezultati: V opazovalnem obdobju je bilo opravljenih 24 meritev minimalne koncentracije ciklosporina v krvi (C_0), v intervencijskem obdobju pa 18. Odzivni čas od meritve do vpisa zdravnikovega mnenja v medicinsko dokumentacijo je v opazovalnem obdobju znašal 17,4 dni, v intervencijskem pa 6,8 dni. V obeh obdobjih petina opravljenih meritev C_0 ni imela zabeleženega zdravnikovega mnenja v medicinsko dokumentacijo. Delež meritev C_0, ki so bile v ustreznem območju, se je v intervencijskem obdobju z 38 % povečal na 67 %, število dni v terapevtskem območju pa s 37,5 na 70 dni.

Zaključek: Z raziskavo smo potrdili pomen terapevtskega spremljanja koncentracij pri optimiziranju zdravljenja s ciklosporinom. Odzivni čas od meritve koncentracije do vpisa zdravnikovega mnenja v medicinsko dokumentacijo se je v intervencijskem obdobju skrajšal, povečalo se je število doseženih ciljnih koncentracij v krvi ter ocena števila dni, ko so bile koncentracije ciklosporina pri bolnikih v terapevtskem območju. Na našem vzorcu bolnikov se je farmakokinetični program DoseMe® izkazal kot uporaben pripomoček.

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1 Introduction

Cyclosporine, also known as cyclosporine A, is a cyclic polypeptide that is classified as an immunosuppressive drug. The key mechanism of its action is reduced interleukin-2 production and decreased interleukin-2 receptor expression, resulting in decreased T lymphocyte activity. Due to its action, it is successfully used in patients after solid-organ and hematopoietic stem-cell transplants; beneficial effects have also been observed in the treatment of numerous autoimmune diseases(1-3).

Cyclosporine is an inhibitor and a substrate of the cytochrome P450 3A4 metabolic enzyme (CYP3A4) and an inhibitor and a substrate of the P-glycoprotein transport enzyme; this is why its pharmacokinetic interactions with other drugs as well as with certain foods are very common(4-6). The CYP3A5 enzyme also plays a role in the metabolism of cyclosporine, but not in all patients. Only individuals

Table 1: Review of drugs and other substances that may cause interactions with cyclosporine (3,4,10-17).

Pharmacokinetic interactions			Pharmacodynamic interactions with nephrotoxic drugs
↓ Conc. of cyclosporine	↑ Conc. of cyclosporine	↑ Conc. of concomitant drugs	synergestic toxic effects on the kidneys
barbiturates	allopurinol	aliskiren	aminoglycosides
bosentan	amiodarone	ambrisentan	amphotericin B
cyclophosphamide	azithromycin	apixaban	histamine H_2 receptor antagonists
phenytoin	danazol	aripiprazole	ciprofloxacin
fibrates	diltiazem	bosentan	fibrates
carbamazepine	erythromycin	dabigatran etexilate	furosemide
modafinil	fluconazole	daunorubicin	melphalan
nafcillin	glipizide	dexamethasone	methotrexate
oxcarbazepine	cholic acid	digoxin	nonsteroidal anti- inflammatory drugs
octreotide	imatinib	diclofenac	tacrolimus
orlistat	itraconazole	doxorubicin	trimethoprim (with sulfamethoxazole)
probucol	carvedilol	dronedarone	vancomycin
rifampin	ketoconazole	etoposide	
sulfadimidine i.v.	clarithromycin	everolimus	
sulfinpyrazone	chloroquine	fentanyl	
terbinafine	colchicine	colchicine	
ticlopidine	contraceptives (hormonal)	quetiapine	
	lercanidipine	lercanidipine	
	methylprednisolone (high doses)	mitoxantrone	
	metoclopramide	nifedipine	
	mifepristone	ranolazine	
	nefazodone	repaglinide	
	nicardipine	rivaroxaban	
	ranolazine	sirolimus	
	verapamil	statins	
	voriconazole		
	protease inhibitors		
St John's wort	grapefruit		
red wine	Seville oranges		

with at least one CYP3A5*1 allele actually express CYP3A5 and synthesize the CYP3A5 protein, which contributes significantly to cyclosporine metabolism in these individuals. This accelerates the metabolism of cyclosporine and it also increases the production of metabolic products, making patients more susceptible to possible nephrotoxic effects (7,8). Pharmacodynamic interactions with nephrotoxic agents are the result of synergistic toxic effects on the kidneys. Examples of the most common interactions with cyclosporine are detailed in Table 1. Cyclosporine metabolism is also affected by certain disease states. One of the most common is acute gastroenterocolitis. The metabolism and excretion of cyclosporine in enterocytes are disturbed, so a larger amount is absorbed into blood (9).

Due to the frequency of concomitant use, interaction with statins is very important. When used concomitantly, cyclosporine can increase the body's exposure to statins by up to 10 times, which increases the risk of myopathies and rhabdomyolysis. According to various databases, it is only reasonable to use fluvastatin (max. 20 mg, 2 times/day), pravastatin (max. 20 mg/day) and rosuvastatin (max. 5 mg/day) concomitantly with cyclosporine (4,10). However, this is contradicted by the statements in the summary of product characteristics of rosuvastatin-containing drugs. They state that the concomitant use of cyclosporine and rosuvastatin is even contraindicated.

Cyclosporine is an active substance with a narrow therapeutic index and high inter- and intraindividual variability of pharmacokinetic parameters, which can result in subtherapeutic as well as toxic concentrations in the patient's blood. Therefore, for effective and safe treatment with cyclosporine, it is necessary to monitor its concentration in blood and to individually adjust the dose to the target concentration range, which is included in the service of Therapeutic Drug Monitoring (TDM) (18-20). This is especially important in organ transplant patients, as insufficient concentrations can result in rejection and graft loss. In patients with autoimmune diseases, blood levels of cyclosporine that are too low pose a risk to the effectiveness of treatment, and concentrations that are too high pose a risk of toxicity. In addition to the regular monitoring of blood concentrations, the safety of cyclosporine treatment must include monitoring renal and hepatic functions and determining values of bilirubin, lipids, potassium, magnesium and uric acid in serum. Regular blood pressure measurements are also required (3,4,10).

Because cyclosporine is unevenly distributed between plasma and the blood cells (33–47% present in plasma, the rest is distributed in different proportions in lymphocytes, granulocytes and erythrocytes), its concentration is determined in whole blood with the addition of an anticoagulant. The timing of the sample collection in relation to the time of the last dose of the drug is important. Most often, the minimum concentration of cyclosporine in the blood is determined, C_0, i.e. the concentration just before the next dose is administered. Extensive data from the literature and the practicality of blood sampling speak in favour of determining C_0 (1,21). The literature also mentions the determination of the maximum concentration of cyclosporine in the blood, C_2, i.e. the concentration two hours after the dose is administered, which is supposed to have a better predictive value in terms of total exposure to the active substance, but subsequent studies have not been able to confirm this. The time when cyclosporine concentration reaches its maximum value after ingestion depends on a number of factors; this is why errors due to a sample taken too quickly or too late are common (22-25). We decide to determine C_2 only in more complex cases, when determining cyclosporine concentration at a single time point does not provide sufficient information on the pharmacokinetics in an individual (26).

For the practical implementation of cyclosporine TDM, we need to identify appropriate therapeutic ranges that serve as guidelines for dosage adjustment. Recommended therapeutic ranges for treatment, collected from various studies and through consultation with experts in this field, can be found in Table 2. Recommended ranges for C_0 and C_2 in the treatment of autoimmune diseases are listed. Therapeutic ranges for individual transplant cases are not listed in the table, as all patients with organ transplants are managed at the University Medical Centre Ljubljana. The target concentration ranges of cyclosporine for these indications are within their competence. The listed recommended ranges are used at the University Medical Centre Maribor as therapeutic ranges for the indications specifically listed here.

Only a limited set of literature is available to obtain information on the therapeutic ranges of cyclosporine in the treatment of various autoimmune diseases. Recommended ranges define the use of various immunochemical methods to determine the concentration of cyclosporine in the blood, in particular fluorescence polarization immunoassay (FPIA). The general therapeutic range for autoimmune diseases is also used in the literature to monitor the concentrations determined using the LC-MS/MS chromatographic method (i.e. liquid chromatography tandem mass spectrometry), which is considered as the gold standard. When using immunochemical methods to determine the concentration of cyclosporine in the blood, the measured values are in most cases falsely higher, which is confirmed by numerous sources in the literature (1,48-52). The most common commercial immunochemical methods for determining cyclosporine and their deviations from the values determined by chromatographic methods are shown in Table 3.

Table 2: Recommended therapeutic ranges for treatment with cyclosporine (1,27-47).

Indications	Therapeutic range	
	C_0 [µg/L]	C_2 [µg/L]
autoimmune diseases (general guidance)	50–150	500–600
polymyositis and dermatomyositis	150	
systemic lupus erythematosus	80–150	
Behçet disease	> 50	
rheumatoid arthritis	50–150	
glomerulonephritis	125–200	
nephrotic syndrome	80–120	
focal segmental glomerulosclerosis	100–200	
aplastic anaemia	150–200	
myelodysplastic syndrome	200	
endogenous uveitis	80–150	
psoriasis	< 200	
atopic dermatitis	no spec. range	

The goal of cyclosporine TDM is to maintain blood concentrations in the recommended range. Values above the upper limit pose a risk of adverse reactions, while concentrations below the lower limit may result in rejection of the transplanted organ in patients after transplantation, and in ineffective treatment in patients with autoimmune diseases. Maintaining blood levels of cyclosporine within the recommended ranges is also important to control side effects, as they are often dose-dependent and responsive to dose reduction. The most common side effects of cyclosporine are acute and chronic kidney failure, liver failure, hypertension, hyperkalaemia, hyperuricaemia, hypomagnesaemia, hypercalciuria, hypophosphatemia, hypercalcaemia, metabolic acidosis (hyperchloremic), tremor, hirsutism, anorexia, diarrhoea, nausea, and vomiting. Due to the cyclosporine's mechanism of action, patients are also at increased risk for onset of infectious diseases and malignant neoplasms (3).

In 2016, we conducted a prospective study at the University Medical Centre Maribor, to test whether a computer-as-

sisted TDM service using the pharmacokinetic software DoseMe® as a clinical pharmacy activity contributes to the optimization of cyclosporine treatment in patients with autoimmune diseases. According to our information, this is the first such study in Slovenia.

2 Materials and methods

2.1 Materials

DoseMe® is a computer software, designed to plan individual dosing of active substances with a narrow therapeutic index and high variability of pharmacokinetic parameters. When calculating the recommended dose, the software operates by utilising the Bayesian theorem, taking into account population pharmacokinetic parameters, patient data (demographic, clinical, therapeutic) and measured blood concentration (53).

To describe the pharmacokinetics of cyclosporine, DoseMe® uses a two-compartment pharmacokinetic model in which the absorption of cyclosporine is determined by the Erlang (gamma) distribution and the elimination is performed by first order kinetics. The model was developed and validated on the population of patients with transplanted organs (kidneys, heart, lungs), which included both adults and paediatric patients; as an important covariate, it includes total body weight (54). The model is useful in optimizing treatment with a newer formulation of cyclosporine (Neoral), which forms a homogeneous microemulsion in the body, the absorption of which is not as dependent on the presence of bile salts as was the original, oil-based formulation of cyclosporine (Sandimmune). Today we only use the newer formulation. The final model has a good predictive value, but should be used with caution in other patient populations, as it has only been validated in the population of organ transplant patients (53,54).

2.2 Methods

We conducted a prospective study, which included all patients who permanently receive cyclosporine due to autoimmune diseases and were treated at the University Medical Centre Maribor as inpatients or outpatients, in the period from the beginning of July to the end of December 2016. Prior to the start of the study, we collected data on the recommended therapeutic ranges of cyclosporine for various indications, which served as guidelines for treatment (Table 2). The study lasted six months, with an observation period in the first half and an intervention period in the last three months. In the first half of the study, we monitored 8 and in the

Table 3: Most common immunoassays for the determination of cyclosporine blood concentrations and their bias (1,48,49).

Immunoassay	Bias (positive)
EMIT	9–13%
CEDIA Plus (cloned enzyme donor immunoassay)	9–12%
CMIA (chemiluminescent microparticle immunoassay)	some studies suggest comparability with chromatographic methods, other quote positive bias up to 15%
ACMIA (antibody conjugated magnetic immunoassay)	12%
FPIA (fluorescence polarization immunoassay)	15–30%

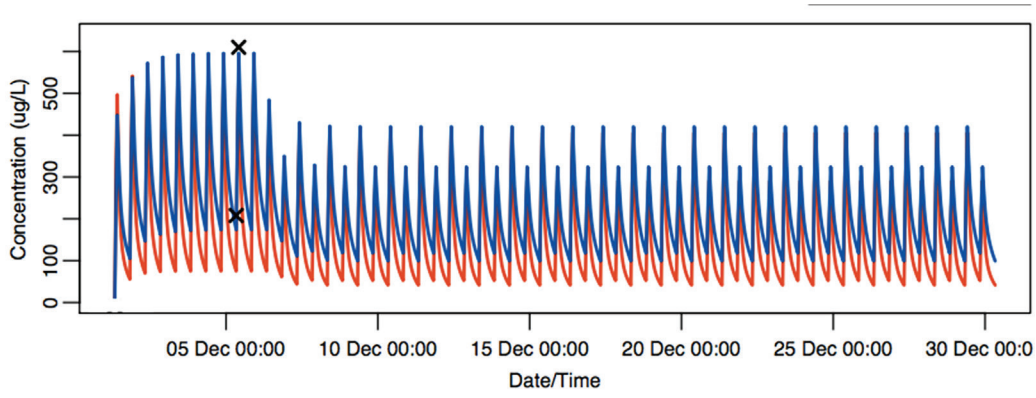

Figure 1: An example of pharmacokinetic profile in DoseMe® software (red curve – population model, blue curve – individual patient, black cross – measured cyclosporine concentration).

second half, 9 patients, 6 of which were monitored in both periods. By monitoring the selected parameters, we compared the success of cyclosporine treatment in both periods. The parameters were: the number of cyclosporine blood concentration measurements; number of measurements, followed by the entry of the doctor's interpretation in the medical documentation; response time from measurement to entry of the doctor's interpretation in the medical documentation; number of measurements within the therapeutic range, number of days when the patient was within the therapeutic range; the number of concomitantly prescribed drugs that may interact with cyclosporine; the number of cases of concomitant ingestion of grapefruit or other, possibly inappropriate substances; the number of clinically significant interactions; the number of presented cyclosporine side effects, which were not results of interaction; and the number of faulty blood samples during laboratory control (due to previous dose intake).

During the observation period, the treatment of all included patients was performed according to an established order; they took the drugs according to the doctor's instructions, they had regular outpatient appointments and gave blood samples for control. If necessary, the doctor adjusted the dosage of cyclosporine. The records of outpatient examinations and the dosing instructions for cyclosporine and other drugs were recorded in the Medis medical documentation program. The clinical pharmacist tested the DoseMe® software during this period.

During the intervention period, we introduced an additional step into the established routine; immediately after determining the cyclosporine blood concentration, the clinical pharmacist performed a simulation in the DoseMe® software and prepared a recommendation for the most appropriate dosing regimen to achieve the desired concentration of the drug in the blood. The doctor, at their discretion, used the recommendation as an adjunct to further dosing.

To use the DoseMe® pharmacokinetic software, we need the patient's basic data, which is entered into the software at the beginning of treatment (gender, age, body weight, body height). We also enter the exact time and the amount of each dose. Based on the entered data, the software plots the concentration curve of cyclosporine in the patient's blood, taking into account population parameters. When the measurement of the actual concentration of cyclosporine in the patient's blood is obtained, the value is entered into the software, which then draws an individual concentration curve, adjusted to the pharmacokinetic parameters of each patient. Both curves and the two measurements of the

patient's cyclosporine concentration (C_0 and C_2) are shown in Figure 1. The Figure shows the deviation of the concentration curve of cyclosporine in the blood of an individual patient from the population curve when it comes to the interaction of cyclosporine with diltiazem.

Once an individual concentration curve is available, the optimal dosing regimen can be calculated for the patient to achieve the desired blood levels of cyclosporine. The date and time of the next dose and the desired concentration of cyclosporine in the blood are entered into the software; the software then prepares a recommendation with the proposed dosing regimen, which can be changed as desired. At the same time, the software calculates the estimated minimum and maximum concentration of cyclosporine in the blood and the total 24-hour exposure (AUC). Basic pharmacokinetic parameters (the volume of distribution, clearance, elimination rate constant, half-life) are also recorded on the recommendation.

Chemical analysis of blood samples was performed by the Department of Laboratory Diagnostics, University Medical Centre Maribor. Cyclosporine blood levels were determined on a Thermo Scientific Indiko Plus analyser, using the CEDIA Plus method.

Minimum blood levels of cyclosporine were monitored in most patients to determine the appropriateness of cyclosporine treatment, and with some patients, the concentration was measured two hours after dosing. Because a simple statistical analysis (paired sample t-test) showed that there was no statistically significant difference in the recommended dose if it was calculated taking into account C_0 and C_2, or merely C_0, we abandoned subsequent measurements of C_2.

Computer programs IBM SPSS Statistics® and Microsoft® Office Excel were used for statistical analysis of the results. The IBM SPSS Statistics® computer program was used to determine statistically significant differences between the calculated ratios in the observation and intervention periods (Pearson's chi-square test), where we assumed independence between the two observed populations. In all statistical tests, we chose the significance level of 0.05 ($\alpha = 0.05$).

The ethical adequacy of the research was confirmed by the Medical Ethics Commiteee of the University Medical Centre Maribor. Patients were informed about the purpose of the study and confirmed their participation with written consent.

3 Results

During the observation period, 8 patients were included in the study and 9 in the intervention period. 6 patients were monitored in both periods. The mean age of the patients in the observation period was 57.3 years (range 45–68 years), and the male to female ratio was 4/4. In the intervention period, the mean age of the patients was 61.3 years (range 45–74 years), and the male to female ratio was 6/3. In terms of mean age, both groups of patients were comparable, while the distribution by gender was more equal in the observation period. We did not include patients with organ transplants in the study, as their immunosuppressive therapy is conducted at the University Medical Centre Ljubljana. In our set of patients, the indications for the use of cyclosporine were the following diseases: primary membranous glomerulonephritis (2 patients), nephrotic syndrome (2 patients), dermatomyositis (2 patients), polymyositis (1 patient), granulomatous myositis (1 patient), systemic lupus erythematosus (1 patient), Behçet's disease (1 patient), aplastic anaemia (1 patient). In total, 4 nephrological, 6 rheumatological and 1 haematological patients were included in the study.

We obtained all the necessary information from the Medis medical documentation program. Table 4 contains a comparison of measured minimum cyclosporine blood concentrations and calculated basic statistical parameters in the observation

and intervention periods, given the individual indications.

We monitored the same parameters in the observation and intervention periods; they are presented in Table 5. For each monitored parameter, a subanalysis is also shown, which includes only patients who were monitored in both periods.

The most important monitored parameter was the number of C_0 measurements that were within the therapeutic range. Statistical analysis showed that despite a noticeable difference in the proportion of relevant measurements, in the observation period 9/24 and in the intervention period 12/18, the difference between the periods was not statistically significant ($p = 0.119$). The proportion of relevant C_0 measurements was followed by an estimate of the next parameter, i.e. the average number of days when the patient's concentrations were within the therapeutic range. The difference between 37.5/90 days (standard deviation 36.0 and confidence interval 37.5 ± 24.9 days) in the observation period and 70/90 days (standard deviation 29.2 and confidence interval 70 ± 19.0 days) in the intervention period is statistically significant ($p < 0.0001$), but it should be noted that the average number of days when the patient's concentrations were within the therapeutic range is used only as an estimate. The difference in the number of C_0 measurements, which were followed by the entry of the doctor's interpretation in the medical documentation, also proved to be statistically insignificant ($p = 1.0$). This is also evident from the results; the share of measurements was practically the same in both periods.

During the intervention period, we prepared 21 recommendations, of which 18 were fully or partially complied with (85.7%). The cases when the doctor chose the same total daily dose as in the recommendation, but did not divide it into two equal individual doses, are considered as partially complied with.

4 Discussion

Table 5 shows the progress achieved in the intervention period compared to the observation period, but due to the small size of the sample we cannot speak of statistically significant differences regarding the most important monitored parameter (number of C_0 measurements within the therapeutic range). By including a multidisciplinary team and by changing the way of communicating the results, we shortened the response time from the measurement to the entry of the doctor's interpretation in the medical documentation. The reason for the long response times in the observation period was that patients sometimes had their blood withdrawn in the laboratory to determine the concentration, but later did not contact a specialist who would interpret the value. During the intervention period, we obtained data on the measured concentrations actively and immediately prepared recommendations, which the doctor then directly received. In this way, data tracking was improved and a faster response was made possible. However, even during the intervention period, with about one-fifth of the measurements, the doctor's response to the measured concentration was not recorded in the medical records. The reason for that were telephone consultations and patient's visits outside the assigned outpatient appointment, which was mostly not recorded.

In the observation period, we observed mainly concentrations of cyclosporine that were too low (12/24 measurements of C_0), compared to the therapeutic ranges that we tried to achieve in the intervention period. In some cases, the clinical condition of the patient was also the reason, as the dose of cyclosporine was not increased in the event of a stable condition or with the occurrence of side effects despite measured concentrations that were too low. The patient's clinical condition was also

Table 4: Comparison of measured minimum cyclosporine blood concentrations and calculated basic statistical parameters.

Indication	Observation period			Intervention period		
	C_0 [1] [µg/L]	statistical parameter		C_0 [µg/L]	statistical parameter	
primary membranous glomerulonephritis	76 65 104	average value	81.7	114 116 165	average value	131.7
		median	76		median	116
		min value	65		min value	114
		max value	104		max value	165
		IQR[2]	19.5		IQR	25.5
nephrotic syndrome	101 118	average value	109.5	121 208	average value	164.5
		median	109.5		median	164.5
		min value	101		min value	121
		max value	118		max value	208
		IQR	8.5		IQR	43.5
polymyositis and dermatomyositis	35 38 49 83	average value	51.3	125 63 56 64	average value	77
		median	43.5		median	63.5
		min value	35		min value	56
		max value	83		max value	125
		IQR	20.3		IQR	18
granulomatous myositis	86 68 78 58	average value	72.5	132 100 140	average value	124
		median	73		median	132
		min value	58		min value	100
		max value	86		max value	140
		IQR	14.5		IQR	20
systemic lupus erythematosus	44 34 118	average value	65.3	/	average value	/
		median	44		median	/
		min value	34		min value	/
		max value	118		max value	/
		IQR	42		IQR	/
Behçet's disease	39 170[3] 224[3] 31	average value	116	25 102	average value	63.5
		median	104.5		median	63.5
		min value	31		min value	25
		max value	224		max value	102
		IQR	146.5		IQR	38.5

Indication	Observation period			Intervention period		
	C_0 [1] [µg/L]	statistical parameter		C_0 [µg/L]	statistical parameter	
aplastic anaemia	221 168 169 191	average value	187.3	270 100[4] 169 175	average value	178.5
		median	180		median	172
		min value	168		min value	100
		max value	221		max value	270
		IQR	29.8		IQR	47
altogether	**average value**		**98.7**	**average value**		**124.7**
	median		**80.5**	**median**		**118.5**
	min value		**31**	**min value**		**25**
	max value		**224**	**max value**		**270**
	IQR		**82.75**	**IQR**		**58.8**

[1] individual measured values of cyclosporine blood concentration
[2] interquartile range
[3] concomitant use of grapefruit
[4] Planned short-term targeting of lower cyclosporine concentrations in patient's blood, due to a sudden elevation in cyclosporine concentration at previous measurement.

taken into account during the intervention period. If the patient's condition was clinically stable and the measured concentration did not deviate significantly from the recommended concentration at the doctor's discretion, the dose was not modified. Even so, the proportion of concentrations that were too low was lower during the intervention period (4/18 of C_0 measurements). An unintentional increase in the concentration of cyclosporine in the patient's blood was observed in one case during the observation period, as a result of concomitant consumption of a grapefruit. The measured cyclosporine blood concentration was five times higher than before. Also during the intervention period, a sudden unintentional increase in cyclosporin blood levels was observed in one case, with the patient reportedly having diarrhoea due to metformin intake. The second case of measured concentration that was too high in the intervention period was recorded with the introduction of cyclosporine therapy in the classical dosing regimen of 2 × 100 mg with the concomitant use of diltiazem in the dose of 3 × 60 mg. This resulted in cyclosporine blood levels that were too high, so we adjusted the therapy accordingly. It is also interesting to note that the occurrence of side effects is not necessarily associated with blood levels of cyclosporine that are too high. Among the observed patients, cyclosporine treatment was better tolerated by men than women. During the observation period, 3 cases of pronounced side effects of cyclosporine were recorded. Two cases involved female patients who, despite subtherapeutic concentrations of cyclosporine in the blood, did not tolerate it, which led to the termination of cyclosporine treatment. The third case was a patient whose cyclosporine blood concentrations were adequate but he nevertheless experienced adverse effects. They disappeared after the treatment was discontinued for a short period of time (14 days). Cyclosporine was then reintroduced. During the intervention period, diltiazem was intentionally administered to 2 patients. Diltiazem increases cyclosporine blood concentrations by inhibiting CYP3A4. Such concomitant treatment

is common in nephrological patients, as the increase in the concentration of the drug in the blood allows for lower doses, while there is also a concurrent reduction of proteinuria, which further prevents the deterioration of renal function. Concomitant statin therapy was better managed during the intervention period, with potentially unsuitable statins being replaced by more appropriate alternatives and with doses adjusted as needed. Atorvastatin or rosuvastatin in the full dose were most commonly prescribed, which is contraindicated in cyclosporine treatment.

The proportion of measured concentrations within therapeutic ranges was our most important observed parameter, with which we evaluated the success of the intervention period and the usefulness of the DoseMe® software. Before the start of the study, we prepared a list of therapeutic ranges and a table with active substances that interact with cyclosporine, and handed them out to all involved doctors. The patients were informed about the purpose of the study before the start of the observation period and were exposed to equal conditions throughout the study. From the patient's point of view, the course of treatment did not change; the only difference between the two periods was the inclusion of a clinical pharmacist and the use of the DoseMe® software, with better results in the intervention period compared to the observation period. The findings suggest the usefulness of the DoseMe® pharmacokinetic software in the individualization of cyclosporine treatment.

The main limitation of the study is its short duration and the low number of

Table 5: Results for the observation and intervention periods.

	Observation period (90 days)	Intervention Period (90 days)
number of patients (M/F)	8 (4/4)	9 (6/3)
patients who were monitored through both periods	*6 (4/2)*	*6 (4/2)*
mean age of patients	57.3 years	61.3 years
patients who were monitored through both periods	*58 years*	*58 years*
mean patients' body weight	79.1 kg	82.2 kg
patients who were monitored through both periods	*81.3 kg*	*81.3 kg*
number of all cyclosporine concentration measurements	30	26
patients who were monitored through both periods	*24*	*16*
number of cyclosporine minimum concentration measurements (C_0)	24	18
patients who were monitored through both periods	*18*	*12*
number of C_0 measurements that were followed by an interpretation	19 (19/24–79%)	15 (15/18–83%)
patients who were monitored through both periods	*14 (14/18–78%)*	*10 (10/12–83%)*
average response time required for a measured concentration to be interpreted[1]	17.4 days	6.8 days
patients who were monitored through both periods	*20.6 days*	*8.4 days*
number of C_0 measurements that were within the therapeutic range[2]	9 (9/24–38%)	12 (12/18–67%)
patients who were monitored through both periods	*8 (8/18–44%)*	*10 (10/12–83%)*

	Observation period (90 days)	Intervention Period (90 days)
average number of days, on which patients' blood levels of cyclosporine were within the therapeutic range (out of whole 90 days)[3]	37.5 days (37.5/90–42%)	70 days (70/90–78%)
patients who were monitored through both periods	*50 days (50/90–56%)*	*75 days (75/90–83%)*
overall number of simultaneously prescribed drugs that may cause an interaction with cyclosporine[4]	6	7
patients who were monitored through both periods	*3*	*2*
combinations of cyclosporine and grapefruit or any other potentially inappropriate substances	1	/
patients who were monitored through both periods	*1*	
number of clinically relevant interactions	1	2[5]
patients who were monitored through both periods	*1*	*0*
number of patients with expressed cyclosporine adverse effects	3[6]	/
patients who were monitored through both periods	*1*	
number of faulty blood samples during laboratory control (due to previous dose intake)	/	2
patients who were monitored through both periods		*2*

[1] The number of days that were needed from the cyclosporine concentration measurement until the first doctor's input into the patient's medical record. For this to happen, first the doctor must be informed about the cyclosporine blood concentration measurement, the measured concentration must be assessed and interpreted, the doctor has to dictate the medical report, which is then typed into the Medis medical record software by a health administrator. For the calculation of the response time in case of a non-interpreted concentration, we used the first input that appeared in the patient's medical record after this measurement, regardless of the number of new concentrations recorded during this time.

[2] Measured concentrations with ± 10% deviations according to the recommended therapeutic ranges were also considered as appropriate. When assessing the appropriateness of measured concentrations, we also took doctor's opinion into consideration.

[3] This is an estimate or interpolation, based on the assumption that as long as two consecutive cyclosporine blood concentration measurements were within the therapeutic range and the dosing regimen as well as the concomitant therapy did not change in the meantime, the patient maintained adequate cyclosporine blood concentrations the whole time. This is also based on the assumption of appropriate patient adherence, which, in our study, was assessed only through a conversation with the patient.

[4] Interaction is marked as X or D in Lexicomp database. Potentially interacting drugs identified were: rosuvastatin, atorvastatin, diltiazem, carvedilol, spironolactone, naproxen sodium, etoricoxib, chloroquine. There were five patients with potentially interacting drugs in their concomitant therapy during the observation period and four patients during the intervention period.

[5] Intentional iatrogenically induced interaction with an intent to elevate cyclosporine blood concentrations and consequently decrease the needed dose of the medicine. In both cases, the interaction was with diltiazem.

[6] Adverse effects were expressed in three patients. The reported adverse effects were: headache, tremor, muscle and joint pain, nausea, weight loss, elevation of blood pressure, gingivitis, gingival hyperplasia.

patients involved. Due to various indications, our observed population was heterogeneous, and at the same time, due to outpatient treatment, the control of patients was lower than it would have been in case of hospitalization. Most of the currently available articles deal with the topic of therapeutic drug monitoring of cyclosporine in patients after transplantation, especially in the field of nephrology. The usefulness of this service has already been recognized, and the dilemmas currently remain mainly in finding the most appropriate time points for blood collection to determine the concentration of cyclosporine in the blood, which best correlates with cyclosporine exposure and consequently with the achievement of therapeutic effects and prevention of side effects. The other currently significant area is the suitability of laboratory methods for determining the cyclosporine blood concentration. It is known that the results obtained by different methods differ from each other. There is no study that specifically addresses the use of a computer pharmacokinetic software in the optimization of cyclosporine treatment. There is also very little information on the use of cyclosporine in autoimmune diseases, so our research treads on new ground and brings important results at the level of a pilot approach.

5 Conclusion

Our study indicated the advantages of optimizing cyclosporine treatment with a pharmacokinetic software, but due to the limited sample size, we cannot speak of statistically significant differences. While examining the results, we can conclude that in the intervention period, we achieved a higher number of concentrations in the therapeutic range, as well as the higher total number of days when we maintained those concentrations in patients. We intend to continue with these activities in the future, as long-term monitoring is of key importance for evaluating the success of the measure. Despite the small number of patients included, the DoseMe® pharmacokinetic software has also shown itself to be a useful tool in the autoimmune patient population. For better patient participation in treatment, we prepared a leaflet with all the essential information about the cyclosporine treatment. Based on the results of the research, we prepared a protocol for dosing and monitoring of cyclosporine concentrations in the blood of patients with autoimmune diseases, which will be included in regular clinical practice at the University Medical Centre Maribor.

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