MALAYSIAN Journal *of* Pharmacy

Original Research Article

Cyclosporine use in post haematopoietic stem cell transplant: Factors affecting the initial cyclosporine concentration and its association with acute graft-versus-host-disease

Choi Jing Herng*, Nur Azrina Binti Muhamad Moosa , Suuria A/P Subramaniam , Lim V Co, Io Shir Hwa

Article Info

Received date: 14 Nov 2022
Accepted date: 03 Dec 2022
Published date: 31 Dec 2022

Keywords: Haematopoietic stem cell transplant, graft-versus-host disease, cyclosporine

ABSTRACT

Background: Cyclosporine (CSA) is required as a prophylaxis of graft-versus-host disease (GVHD) following allogeneic haematopoietic stem cell transplant (HSCT). However, subtherapeutic CSA concentration will increase the incidence of acute GVHD which is one of the major concerns. **Objective:** This study aims to identify the incidence of patients who achieved therapeutic initial CSA level with a standard intravenous CSA dose of 1.5 mg/kg BD, the occurrence of acute GVHD and factors associated with subtherapeutic CSA initial concentration in post-HSCT patients. **Method:** A retrospective single-centred study was conducted which involved 69 patients who underwent allogeneic HSCT between January 2020 and December 2020 in Hospital Ampang. The factors assessed were patients' demographics, concurrent medications, liver and renal functions. Mann-Whitney test, Kruskal Wallis test and Spearman correlation test were used to identify the factors associated with sub-therapeutic CSA initial concentration. **Result:** 17.4% had therapeutic initial CSA level (200-400 ng/mL) and among 69 patients, 37.7% of them developed acute GVHD post-transplantation. Besides, only ethnicity and serum creatinine significantly affected the initial CSA levels. There was no significant association between the initial CSA level and the occurrence of acute GVHD. **Conclusion:** With the standard intravenous CSA dose of 1.5 mg/kg BD, only 17.4% were able to achieve a therapeutic initial CSA level due to the drug pharmacokinetic variability in different individuals. Hence, this study served as a baseline study for the future prospective clinical study to develop a population pharmacokinetic model in optimising the intravenous CSA dose to achieve the desired therapeutic range and improve the transplant outcomes.

INTRODUCTION

Haematopoietic stem cell transplant (HSCT) is a curative, highly specialised treatment for managing numerous malignant and non-malignant diseases [1]. This process involves the intravenous infusion of haematopoietic stem cells to replace the unhealthy blood cells and rebuild normal blood cell production. Although HSCT has been an effective treatment option for haematologic diseases such as leukaemia and lymphoma, the procedure has potentially high treatment-related mortality, such as graft-versus-host disease (GVHD) development that happens in allogeneic HSCT where the recipient T cells recognise the host as foreign [2]. This scenario directly affects by limiting the success of a potentially curative transplant. Therefore, immunosuppressive treatment is required as a prophylaxis of GVHD following allogeneic HSCT.

The most common GVHD prophylaxis post-allogeneic HSCT has been based on a calcineurin inhibitor, cyclosporine (CSA), together with a short course of methotrexate (MTX) [1]. Despite the long history of this regimen, there are uncertainties about its dosing due to the narrow CSA therapeutic index and its complicated pharmacokinetics which show marked inter

*Correspondence: cjherng1205@yahoo.com.my
DOI: 10.52494/RIPY4395

Department of Pharmacy, Hospital Ampang, Ministry of Health Malaysia, Jalan Mewah Utara, Taman Pandan Mewah, 68000 Ampang Jaya, Selangor, Malaysia.

and intra-patient variability [3]. Hence, the dose, target blood level, and infusion schedule varies among facilities and protocols, and different practices make data generalisation for specific populations impossible [4].

Multiple studies have demonstrated that a subtherapeutic initial CSA concentration would increase the incidence of grade 2-4 and acute GVHD [2,5–7], which is a significant complication of HSCT and a major cause of treatment-related mortality [8]. There is no previous study conducted in Malaysia to address this issue. The current study aimed to identify the incidence of patients who achieved therapeutic initial CSA level with standard intravenous CSA dose, the occurrence of acute GVHD, and the factors associated with subtherapeutic CSA initial concentrations in patients undergoing HSCT.

METHOD

This study was conducted retrospectively at Hospital Ampang, a tertiary hospital known as one of the largest haematology centres in Malaysia where various types of chemotherapy and transplantation are conducted, including allogeneic HSCT. The study was carried out upon approval by the National Medical Research Register (NMRR) and Medical Research & Ethics Committees of Malaysia (MREC) with ID NMRR-21-1705-60857.

All patients who undergoing allogeneic HSCT received intravenous CSA beginning on Day-1 of transplantation with a dose of 3 mg/kg in 2 divided doses by intravenous infusion for the prophylaxis of GVHD post-transplantation. Based on Ampang Hospital Haematology Protocol, the initial targeted concentration of CSA should be around 200 ng/mL [9], and a titration of 25 mg/dose will be given to the patient if the first dose of 3 mg/kg/day does not reach the therapeutic concentration. The initial CSA level was resampled at least on the third day after dose adjustment since the duration for CSA to reach a steady state was around 3-5 days.

Since CSA requires therapeutic drug monitoring (TDM), a list of potential patients was identified from the Hospital Ampang patient TDM database. The patients' medical records were traced using the patients' registration numbers and retrieved from the hospital medical record archive and the electronic-Hospital Information System (e-His). Patient who underwent allogeneic HSCT and received intravenous CSA for the first time between January 2020 and December 2020 in Hospital Ampang were included in the study while patients who have CSA allergy and paediatric patients aged 12 years old and below were excluded from the study.

There were 71 HSCT patients on CSA for the first time within the sampling period, and 69 of these patients met the study inclusion criteria. By setting the margin of error to 5% and a confidence level of 95%, the Raosoft® sample size calculator was used to calculate the sample size, and the recommended minimum sample size was 61 patients. Since the sample size calculated was small, all 69 patients were included in our study.

Demographic and clinical data of patients were obtained from both e-HIS and hospital medical record archives over four months from August to November 2021. Patients' data, including age, gender, body weight, height, serum creatinine (SCr), alanine aminotransferase (ALT), concurrent medications, CSA dose, initial CSA level, presence of acute GVHD and GVHD sites were collected. Serum creatinine and ALT levels on Day-1 of transplantation were collected where intravenous CSA was administered on the same day. Only data on antibiotics, antivirals and antifungals were recorded for concurrent medications, as Stockley's Drug Interaction Checkers showed that these medications potentially interacted with CSA. Data privacy and confidentiality were guaranteed as the names of patients were not collected, and the data collected was kept on a password-protected database that only researchers could access the database.

The primary outcome of this study was to identify the incidence of patients who achieved therapeutic initial CSA level with standard intravenous CSA dose and the occurrence of acute GVHD in post-transplantation patients. In addition, the secondary outcome was to identify the factors associated with sub-therapeutic initial CSA concentration in patients undergoing HSCT. The IBM SPSS® for Windows version 22 was used for analysing the collected through statistical analysis. Categorical data in our study included gender, ethnicity, ALT level, concurrent medications, acute GVHD and its sites, while the numerical data included age, weight, height, SCr and creatinine clearance (CrCL). The descriptive analysis was then used to analyse the categorical and numerical data and presented in terms of frequency, percentage, median and interquartile range.

Before inferential statistical analysis, the normality test was conducted and it was found that data generated in this study were not normally distributed. Thus, non-parametric tests were applied for data analysis. To identify the factors associated with sub-therapeutic CSA initial concentration, the Mann-Whitney test and Kruskal Wallis test were used to analyse the difference of median initial CSA levels between different groups of categorical data, as mentioned above. In contrast, the Spearman correlation test was used for analysing the correlation between the median initial CSA levels and different numerical data such as age, weight, height, and SCr. The strength of correlation was measured by the absolute value of correlation coefficient (*r*), 0.00-0.19 was regarded as "very weak", 0.20-0.39 as "weak", 0.40-0.59 as "moderate", 0.60-0.79 as "strong" and 0.8-1.0 as

a "very strong" correlation [10]. Besides, a Chi-square test was applied to identify the frequencies of acute GVHD between the two CSA level groups (<200 ng/mL and 200-400 ng/mL). A *p*-value of <0.05 for the two-tail test was considered statistically significant.

RESULTS

In this study, the baseline demographic and clinical characteristics of 69 patients were collected, and the data were summarised as shown in **Table I**. There were slightly more female patients than male patients, with 52.2% and 47.8%, respectively. Besides, more than half of the patients were Malay (68.1%), followed by Chinese (18.8%), Indian (8.7%) and others (4.3%). The median age, weight and height of the patients were 32 years old (IQR: 22.00), 66 kg (IQR: 21.50) and 162 cm (IQR: 12.50).

Table I: Demographic and clinical characteristics of patients (n=69)

Demographic and clinical characteristics	n	(%)
Gender		
Male	33	(47.8)
Female	36	(52.2)
Ethnicity		
Malay	47	(68.1)
Chinese	13	(18.8)
Indian	6	(8.7)
Others	3	(4.3)
Age (years)	32	(22.00)*
Weight (kg)	66	(21.50)*
Height (cm)	162	(12.50)*
ALT (U/L)		
Normal	56	(81.2)
High	13	(18.8)
SCr (umol/L)	49	(24.00)*
CrCL (mL/min)	147	(103.50)*
Concurrent antibiotics		
Ciprofloxacin	63	(91.3)
Ciprofloxacin & Sulfamethoxazole/Trimethoprim	6	(8.7)
Concurrent antifungals		
Fluconazole	54	(78.3)
Amphotericin	6	(8.7)
Micafungin	9	(13.0)
Concurrent antivirals		
Acyclovir	63	(91.3)
Acyclovir & Ganciclovir	6	(8.7)
Initial CSA level (ng/mL)		
<200	53	(76.8)
200-400	12	(17.4)
>400	4	(5.8)
Presence of acute GVHD		
Yes	26	(37.7)
No	43	(62.3)
GVHD site		
Skin	7	(26.9)
Gut	7	(26.9)
Liver	3	(11.5)
Ocular	1	(3.9)
≧ 2 sites	8	(30.8)

*** Median (IQR)**

Table II: Factors associated with subtherapeutic initial CSA levels (n=69)

Demographic and clinical characteristics	Initial CSA level (ng/mL) Median (IQR)		Spearman correlation, *r*	*p*-value
Gender				
Male	150.30	(99.25)		0.627[b]
Female	138.75	(103.98)		
Ethnicity				
Malay	156.20	(105.00)		0.030[a*]
Chinese	103.40	(66.80)		
Indian	132.15	(390.75)		
Other	60.00	(77.50)		
Age (years)			-0.061	0.619[c]
Weight (kg)			0.168	0.167[c]
Height (cm)			0.060	0.624[c]
ALT (U/L)				
Normal	138.75	(84.98)		0.061[b]
High	184.50	(161.80)		
SCr (umol/L)			0.257	0.033[c*]
CrCL (mL/min)			-0.064	0.602[c]

[a] Kruskal Walli's test. X^2 statistics (df) = 8.975(3). Post hoc multiple comparisons test: Malay vs Chinese, p = 0.039 (Bonferroni correction of p-value)
[b] Mann-Whitney test
[c] Spearman correlation
*** The p-value of less than 0.05 (p<0.05) was considered to be significant**

A large portion of patients (81.2%) had normal ALT levels. The median SCr value was reported as 49 umol/L (IQR: 24.00), while the median CrCL value was 147 mL/min (IQR: 103.50). For concurrent medications, 91.3% of patients took ciprofloxacin as antibiotic prophylaxis, and the rest took two types of antibiotics (ciprofloxacin and sulfamethoxazole/trimethoprim). This percentage distribution was the same for patients who took different types of antivirals (acyclovir and ganciclovir). Meanwhile, 78.3%, 8.7% and 13.0% of patients took fluconazole, amphotericin and micafungin, respectively as anti fungal prophylaxis.

Furthermore, a majority of patients (76.8%) had sub-therapeutic initial CSA levels of <200 ng/mL while 17.4% achieved the therapeutic range of 200-400 ng/mL, followed by 5.8% who achieved >400 ng/mL. Among 69 patients, 37.7% of them developed acute GVHD post-transplantation, and the GVHD sites reported were skin (26.9%), gut (26.9%), liver (11.5%), ocular (3.9%) and more than two areas (30.8%).

Overall, the median initial CSA level was reported as 147.4 ng/mL (IQR: 97.15), and the Mann-Whitney test was conducted to determine whether there was a difference in initial CSA levels in patients with different demographics and clinical characteristics. Based on **Table II**, the results of the Mann-Whitney test showed that there was no significant difference in median initial CSA levels between male and female patients, z = -0.487, p-value = 0.627 and also between those with normal and high ALT levels, z = -1.872, p-value = 0.061. Meanwhile, there was a significant difference in the median initial CSA levels among the four ethnicity groups (X^2

statistics (*df*) = 8.975(3)). Post hoc analysis using multiple comparisons showed that there was a significant difference in median initial CSA levels between Malay and Chinese groups (*p*-value= 0.030). *P*-value was Bonferroni adjusted. Malay patients had significantly higher median initial CSA levels (156.20 ng/mL (IQR= 105.00)) compared to Chinese patients (103.40 ng/mL (IQR= 66.80)). However, there was no significant difference between other ethnicity groups. Furthermore, the correlations between the initial CSA level and age, weight, height and CrCL of the patients were found to be very weak and statistically insignificant, with *p*-values of 0.619, 0.167, 0.624 and 0.602, respectively. At the same time, there was a weak positive correlation (r = 0.257) between the initial CSA levels and SCr with a *p*-value of 0.033, which suggested that the initial CSA levels increased significantly with serum creatinine.

Besides, the concurrent antibiotics, antifungals and antivirals that the patient took along with intravenous CSA were also recorded in this study for further analysis. The difference in initial CSA level among patients taking the different groups of concurrent medications was analysed through the Mann-Whitney and Kruskal Wallis tests respectively. The results of both tests was summarised in **Table III.** There was no significant differences in initial CSA levels between different antibiotics, antifungals and antivirals groups with *p*-values of more than 0.05.

Table III: Difference between concurrent medications and initial CSA level (n=69)

Concurrent medications	Initial CSA level (ng/mL) Median (IQR)		*p*-value
Antibiotics			
Ciprofloxacin	150.30	(113.60)	0.539[a]
Ciprofloxacin & Sulfamethoxazole/Trimethoprim	129.40	(38.32)	
Antifungals			
Fluconazole	148.85	(89.63)	0.840[b]
Amphotericin	130.90	(285.50)	
Micafungin	147.40	(339.55)	
Antivirals			
Acyclovir	152.80	(109.30)	0.079[a]
Acyclovir & Ganciclovir	121.60	(63.55)	

[a] **Mann-Whitney test** [b] **Kruskal Wallis test**

Table IV: Association between initial CSA level and presence of acute GVHD (n=69)

Presence of acute GVHD	Initial CSA level < 200 ng/mL, n (%)	Initial CSA level ≧ 200 ng/mL, n (%)	X^2 (*df*)	*p*-value
Yes	20 (76.9)	6 (23.1)	0.000 (1)	>0.950[a]
No	33 (76.7)	10 (23.3)		

[a]**Chi-square test**

In this study, the number of patients who developed acute GVHD post-transplantation was also recorded, and its association with the initial CSA levels was identified through a Chi-square test, and the result was tabulated in **Table IV**. Although the association was not statistically significant, X^2 (1, n=69) = 0.000, *p*-value >0.950, there were 20 patients with an initial CSA level of <200 ng/mL (76.9%) developed acute GVHD as compared to only six patients with an initial CSA level of ≧200 ng/mL (23.1%).

DISCUSSION

To our knowledge, this is the first retrospective study investigating the factors affecting the initial CSA levels and its association with the occurrence of acute GVHD among the Malaysian allogeneic HSCT patients in Hospital Ampang, one of the well-known haematology centres where patients with haematology-related illness are referred to here for various chemotherapy and transplantations.

In this study, with the current standard dose of intravenous CSA 1.5 mg/kg BD and the method of rounding the dose to the nearest 25 mg, most of the patients (76.8%) had sub-therapeutic initial CSA levels of <200 ng/mL and the least number of patients (5.8%) had achieved initial CSA levels of >400 ng/mL. Based on previous studies, demographic and clinical factors such as age, gender, liver and renal functions and drug-drug interactions were reported to contribute to Different initial CSA levels among each individual [11–13], and the influence of these factors in our study sample would be discussed further in the following paragraphs. Besides, sampling error might also be one of the factors, as other study suggested avoiding sampling or sample interpretation in the first hour of infusion where inconsistent results had been reported [14].

Next, factors affecting the initial CSA levels were also identified in our study. Firstly, no significant difference in initial CSA level was found between male and female HSCT patients (*p*-value = 0.627), and the current research supported the results of 2 previous studies [11,15]. However, some researchers have shown that gender significantly affects the CSA pharmacokinetics in solid organ transplant patients [16–18]. These conflicting results of gender effect on initial CSA levels might be explained by the interindividual variation of P-glycoprotein expression and CYP3A activity regardless of gender [16].

Moreover, it was reported in a previous study that clearance of CSA decreased with increasing age; therefore, initial CSA levels varied across paediatric, adult and geriatric populations [13,16,19]. Nonetheless, age was not significantly correlated with initial CSA level in this study and this outcome was possible because only the adult population with a median age

of 32 years old (IQR: 22.00) was involved in this study, and no significant difference was found among this population. Previous studies supported our findings that age did not significantly affect the CSA pharmacokinetics compared to the paediatric population [20,21].

The correlation between initial CSA level and weight was also evaluated in this study, but it was found to be statistically insignificant, which was opposed the previous studies that body weight was significantly associated with CSA clearance and its level [14,21–24]. Consistently, height was insignificantly correlated with the initial CSA level , parallel to other studies [11].

Limited studies were conducted to analyse ethnicity's association with CSA pharmacokinetics. In Malaysia, a retrospective study conducted among solid organ transplantation patients did not show an effect of ethnicity on CSA pharmacokinetics [16]. However, a statistically significant difference in the initial CSA level between Malay and Chinese patients was demonstrated in our study. Currently, evidence on the effect of CSA clearance among different ethnicities in Malaysia is still lacking. However, it had been previously demonstrated in a foreign study that CSA clearance was higher in white patients than in black and Asian patients, suggesting that different ethnic groups had different CSA levels [25].

Besides, the normal range of ALT was defined as between 4-36 U/L [26] and patients were classified into two groups (normal and high ALT levels). This finding was contrary to other studies which showed CSA was extensively metabolised by the liver and that liver function altered CSA pharmacokinetics [11,12]. The difference in initial CSA level between normal and high ALT groups in this study was reported to be insignificant.

Furthermore, the current study showed that initial CSA levels increased significantly with SCr, which contrasts with previous studies that reported an insignificant effect of SCr on initial CSA levels [11,24,27]. Generally, SCr and CrCL yielded a reasonable estimation of renal function, but CrCL provided a more accurate assessment as it was adjusted based on parameters such as age, gender, body weight and height [28]. Due to limited patient numbers and short study duration in the current study, these parameters were not found to affect the initial CSA level significantly; thus, CrCL showed a similar finding.

In addition, infections were the major cause of morbidity and mortality after transplantation; thus, antimicrobial agents were widely used in patients who had received transplantation [29]. As drug-drug interaction might affect the pharmacokinetics of CSA and its serum level, its influence on the initial CSA level was also analysed statistically in this study. Nonetheless, the difference in initial CSA levels between different antibiotics, antifungals and antivirals groups was statistically insignificant. With the exception that antifungals such as micafungin and antivirals showed a similar result to the previous study [30], other groups of antimicrobial agents showed opposing findings to previous studies and Stockley's Drug Interaction Checkers [14,20,30–32].

During data collection, although it was necessary to report the grades of acute GVHD to determine its severity, only the occurrence site of acute GVHD was collected as the grade of acute GVHD was not recorded in patients' clinical notes and bed head tickets (BHT). The current study reported that among 69 patients, 37.7% of them developed acute GVHD post-transplantation and the acute GVHD area reported were skin (26.9%), gut (26.9%), liver (11.5%), ocular (3.9%) with 30.8% patients reporting multiple sites involvement. The association between the initial CSA level and the presence of acute GVHD was also assessed in this study to justify the impact of the initial CSA level in causing acute GVHD and further Deteriorating the patient's health. The result showed that the association was not statistically significant, which was inconsistent with previous studies [4,33,34].

Despite the result being statistically insignificant, 76.9% of patients with an initial CSA level of <200 ng/mL developed acute GVHD compared to only 23.1% with an initial CSA level of ≧200 ng/mL. Besides, a study reported that maintaining CSA trough levels of ≧200 ng/mL resulted in a lower incidence of acute GVHD in the following weeks and found significant benefits of maintaining a higher serum concentration of CSA in the minimisation of acute GVHD [5]. Moreover, it was essential to prevent acute GVHD as the cost of treating GVHD was much higher compared to the cost of preventing GVHD. GVHD as a retrospective analysis of hospital data reported higher hospital readmission rates and associated costs following HSCT among patients with acute GVHD compared with those without GVHD, and the readmission rate and costs increased with the severity of acute GVHD [35]. Another retrospective study summarised that patients with acute GVHD had a longer length of stay, a higher ICU admission rate, and a higher median total cost compared with patients with no GVHD during initial hospitalisation for HSCT and experienced higher rates of hospital readmission and inpatient mortality during the 100 days following HSCT [36].

Our study was limited by its retrospective nature and the fact that it included patients from a single medical centre. Differences in the composition of patient cohorts among various centres prevented us from making general conclusions regarding initial CSA levels, factors affecting it and its association with the occurrence of acute GVHD. Moreover,

time constraints limited our sample size as we only included data in a year due to the time-consuming process of obtaining the manual patient medical record from the hospital archive.

CONCLUSION

In conclusion, therapeutic drug monitoring was crucial in designing patient-specific CSA dosage regimens as with the current standard dosing method. We found that there was only a small portion of patients could achieve therapeutic initial CSA levels due to the drug pharmacokinetic variability in different individuals. In this study, only ethnicity and SCr were found to affect the initial CSA level significantly. However, our findings should not be generalised due to the limitations of the small sample size from a single centre. Last but not least, even though we did not prove the significant benefits of maintaining an initial CSA level at the therapeutic range in minimisation of acute GVHD, it served as a baseline study for a future prospective clinical study to develop a population pharmacokinetic model in optimising the intravenous CSA dose to achieve the desired therapeutic range and maximise the transplant outcomes.

ACKNOWLEDGEMENT

We would like to thank the Director General of Health Malaysia for his permission to publish this article. We would also like to acknowledge Tuan Fauziah Binti Tuan Rosli, a pharmacist at Hospital Ampang, for her assistance in this research's statistical analysis.

REFERENCE

[1] Davulcu EA, Vural F. Immunosuppressive agents in hematopoietic stem cell transplantation. Trends Transplant. 2018;11(1):27–9.

[2] García Cadenas I, Valcarcel D, Martino R, Piñana JL, Barba P, Novelli S, et al. Impact of cyclosporine levels on the development of acute graft versus host disease after reduced-intensity conditioning allogeneic stem cell transplantation. Mediators Inflamm. 2014;2014. https://doi.org/10.1155%2F2014%2F620682

[3] Schiff J, Cole E, Cantarovich M. Therapeutic monitoring of calcineurin inhibitors for the nephrologist. Clin J Am Soc Nephrol. 2007;2(2):374–84. https://doi.org/10.2215/cjn.03791106

[4] Rogosheske JR, Fargen AD, Defor TE, Warlick E, Arora M, Blazar BR, et al. Higher therapeutic CsA levels early post-transplantation reduce risk of acute GVHD and improves survival. Bone Marrow Transplant. 2014;49(1):122–5. https://doi.org/10.1038/bmt.2013.139

[5] Zeighami S, Hadjibabaie M, Ashouri A, Sarayani A, Khoee SH, Mousavi S, et al. Assessment of cyclosporine serum concentrations on the incidence of acute graft versus host disease post hematopoietic stem cell transplantation. Iran J Pharm Res. 2014;13(1):305–12. https://pubmed.ncbi.nlm.nih.gov/24734085/

[6] Malard F, Szydlo RM, Brissot E, Chevallier P, Guillaume T, Delaunay J, et al. Impact of Cyclosporine-A Concentration on the Incidence of Severe Acute Graft-versus-Host Disease after Allogeneic Stem Cell Transplantation. Biol Blood Marrow Transplant [Internet]. 2010;16(1):28–34. Available from: http://dx.doi.org/10.1016/j.bbmt.2009.08.010

[7] Chung EK, Yee J, Kim JY, Gwak HS. Low cyclosporine concentrations in children and time to acute graft versus host disease. BMC Pediatr 2020;20(1):1–6. https://doi.org/10.1186/s12887-020-02125-6

[8] Ponce DM, Gonzales A, Lubin M, Castro-Malaspina H, Giralt S, Goldberg JD, et al. Graft-versus-Host Disease after Double-Unit Cord Blood Transplantation Has Unique Features and an Association with Engrafting Unit-to-Recipient HLA Match. Biol Blood Marrow Transplant [Internet]. 2013;19(6):904–11. Available from: http://dx.doi.org/10.1016/j.bbmt.2013.02.008

[9] Haematology department. AMPANG HOSPITAL HAEMATOLOGY Ampang Protocol. 2012.

[10] Armitage P BG. Statistical Methods in Medical Research. 3rd edition. Oxford: Blackwell Scientific Publications; 1994. 312–41 p. http://196.188.170.250:8080/jspui/bitstream/

[11] Jacobson PA, Ng J, Green KGE, Rogosheske J, Brundage R. Posttransplant Day Significantly Influences Pharmacokinetics of Cyclosporine after Hematopoietic Stem Cell Transplantation. 2003; 311:304–11. https://doi.org/10.1016/s1083-8791(03)00076-4

[12] Wu et al. Population pharmacokinetics of cyclosporine in clinical renal transplant patients. Drug Metab Dispos. 2005;33(9):1268–75. https://doi.org/10.1124/dmd.105.004358

[13] Tafazoli A. Cyclosporine use in hematopoietic stem cell transplantation: Pharmacokinetic approach. Immunotherapy. 2015;7(7):811–36. https://doi.org/10.2217/imt.15.47

[14] Han K, Pillai VC, Venkataramanan R. Population pharmacokinetics of cyclosporine in transplant recipients. AAPS J. 2013;15(4):901–12. https://doi.org/10.1208/s12248-013-9500-8

[15] Aros CA, Ardiles LG, Schneider HO, Flores CA, Alruiz PA, Jerez VR, et al. No gender-associated differences of cyclosporine pharmacokinetics in stable renal transplant patients treated with diltiazem. Transplant Proc. 2005;37(8):3364–6. https://www.academia.edu/13629755/

[16] Albitar O, Ballouze R, Harun SN, Mohamed Noor DA, Sheikh Ghadzi SM. Population Pharmacokinetic Modeling of Cyclosporine Among Malaysian Renal Transplant Patients: An Evaluation of Methods to Handle Missing Doses in Conventional Drug-Monitoring Data. J Clin Pharmacol. 2020;60(11):1474–82. https://doi.org/10.1002/jcph.1670

[17] Fruit D, Rousseau A, Amrein C, Rollé F, Kamar N, Sebbag L, et al. Ciclosporin population pharmacokinetics and bayesian estimation in thoracic transplant recipients. Clin Pharmacokinet. 2013;52(4):277–88. https://doi.org/10.1007/s40262-013-0037-x

[18] Tornatore KM, Brazeau D, Dole K, Danison R, Wilding G, Leca N, et al. Sex differences in cyclosporine pharmacokinetics and abcb1 gene expression in mononuclear blood cells in African American and caucasian renal transplant recipients. J Clin Pharmacol. 2013;53(10):1039–47. https://doi.org/10.1002/jcph.123

[19] Falck P, Åsberg A, Byberg KT, Bremer S, Bergan S, Reubsaet JLE, et al. Reduced elimination of cyclosporine in elderly (>65 Years) kidney transplant recipients. Transplantation. 2008;86(10):1379–83. https://doi.org/10.1097/tp.0b013e31818aa4b6

[20] Li T, Hu L, Ma X, Huang L, Liu X, Luo X, et al. Population pharmacokinetics of cyclosporine in Chinese children receiving hematopoietic stem cell transplantation. Acta Pharmacol Sin [Internet]. 2019;(June). Available from: http://dx.doi.org/10.1038/s41401-019-0277-x

[21] Ni S, Zhao W, Wang J, Zeng S, Chen S, Jacqz-aigrain E, et al. Population pharmacokinetics of ciclosporin in Chinese children with aplastic anaemia : effects of weight, renal function and stanozolol administration. Nat Publ Gr.2013;969–75. https://doi.org/10.1038%2Faps.2013.9

[22] Gupta A, Punatar S, Gawande J, Mathew L, Kannan S, Khattry N. Analysis of factors affecting initial cyclosporine level and its impact on post-transplant outcomes in acute leukaemia. J Cancer Res Ther. 2017;13(6):981. https://doi.org/10.4103/0973-1482.157338

[23] Chen X, Yu X, Wang D, Xu H, Li Z. Initial dosage optimisation of ciclosporin in pediatric Chinese patients who underwent bone marrow

transplants based on population pharmacokinetics. Exp Ther Med. 2020;20(1):401–8. https://doi.org/10.3892%2Fetm.2020.8732

[24] Kim MG, Kim IW, Choi B, Han N, Yun HY, Park S, et al. Population Pharmacokinetics of Cyclosporine in Hematopoietic Stem Cell Transplant Patients: Consideration of Genetic Polymorphisms. Ann Pharmacother.2015;49(6):622–30. https://doi.org/10.1177/1060028015577798

[25] Pourfarziani V, Nemati E, Taheri S, Khoddami-Vishte HR, Azizabadi Farahani M. Satisfactory outcome despite low 2-hour postdose cyclosporine level in Iranian kidney recipients. Iran J Kidney Dis. 2008;2(2):99-101. https://pubmed.ncbi.nlm.nih.gov/19377217/

[26] Pincus MR, Tierno PM, Gleeson E, Bowne WB BM. Henry's Clinical Diagnosis and Management by Laboratory Methods. 23rd ed. St Louis: Elsevier Inc.; 2017. chap 21.

[27] Willemze AJ, Cremers SC, Schoemaker RC, Lankester AC, Den Hartigh J, Burggraaf J, et al. Ciclosporin kinetics in children after stem cell transplantation. Br J Clin Pharmacol. 2008;66(4):539–45. https://doi.org/10.1111%2Fj.1365-2125.2008.03217.x

[28] Nankivell BJ. Creatinine clearance and the assessment of renal function. Aust Prescr [Internet]. 2001; 24:15-7. Available from: https://doi.org/10.18773/au

[29] Paterson DL, Singh N. Interactions between tacrolimus and antimicrobial agents. Clin Infect Dis. 1997;25(6):1430–40. https://doi.org/10.1086/516138

[30] Inoue Y, Saito T, Ogawa K, Nishio Y, Kosugi S, Suzuki Y et al. Drug interactions between micafungin at high doses and cyclosporine A in febrile neutropenia patients after allogeneic hematopoietic stem cell transplantation. Int J Clin Pharmacol Ther. 2012;50(11):831–7. https://doi.org/10.5414/cp201738

[31] Kimura S, Oshima K, Okuda S, Sato K, Sato M, Terasako K, et al. Pharmacokinetics of CsA during the switch from continuous intravenous infusion to oral administration after allogeneic hematopoietic stem cell transplantation. Bone Marrow Transplant. 2010;45(6):1088–94. https://doi.org/10.1038/bmt.2009.316

[32] Sańchez-Ortega I, Vázquez L, Montes C, Patiño B, Arnan M, Bermúdez A, et al. effect of posaconazole on cyclosporine blood levels and dose adjustment in allogeneic blood and marrow transplant recipients. Antimicrob Agents Chemother. 2012;56(12):6422–4. https://doi.org/10.1128%2FAAC.01489-12

[33] Nuechterlein B, Peltz A, Drake K, Finnerty M, Keating A, Craddock J, et al. Optimising Cyclosporine Dosing Regimen to Achieve Therapeutic Levels at the Time of Allogeneic Bone Marrow Transplantation: A Pediatric Quality Improvement Intervention. Biol Blood Marrow Transplant. https://doi.org/10.1016/j.bbmt.2012.11.337

[34] Park S, Kim K, Jang JH, Kim SJ, Kim WS, Jung CW. Blood concentration of cyclosporine during early post-transplant period may have influence on the occurrence of chronic graft versus host disease in patients who received allogeneic hematopoietic stem cell transplantation. Oncotarget 2016;7(37):59892–901. https://doi.org/10.18632/oncotarget.10988

[35] Dignan FL, Potter MN, Ethell ME, Brennan J, McNamara L, Evans SO, Dearden CE, Davies FE, Morgan GJ SB. High Readmission Rates Are Associated with a Significant Economic Burden and Poor Outcome in Patients with Grade ¾ Acute GvHD. Blood. 2011;118(21):2061. https://doi.org/10.1111/ctr.12065

[36] Yu J, Judy JT, Parasuraman S, Sinha M, Weisdorf D. Inpatient Healthcare Resource Utilisation, Costs, and Mortality in Adult Patients with Acute Graft-versus-Host Disease, Including Steroid-Refractory or High-Risk Disease, following Allogeneic Hematopoietic Cell Transplantation: HCRU, Costs, and Mortality Associated with Acute GVHD. Biol Blood Marrow Transplant. 2020;26(3):600–5. https://doi.org/10.1016/j.bbmt.2019.10.028