LINK BETWEEN CYCLOSPORIN EXPOSURE IN TISSUES AND GRAFT VERSUS HOST DISEASE IN PAEDIATRIC BONE MARROW TRANSPLANTATION: ANALYSIS BY A PBPK MODEL

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Objectives

In bone marrow transplantation (BMT), cyclosporin is used to prevent the graft versus host disease (GVHD). A retrospective analysis of clinical data showed different patterns of cyclosporin anti-GVHD effect depending on its mode of administration. Non-linearity in cyclosporin distribution may be an explanation. The objective of this study was to link the occurrence of GVHD to cyclosporin exposure in blood, target organs of GVHD (skin, liver and intestine) and also bone marrow and thymus (effect of cyclosporin on T lymphocytes).

Methods

Using a PBPK model of cyclosporin disposition in children (see companion poster), AUC in blood and organs were calculated for 61 paediatrics patients (31 with intermittent 2 h every 12 h infusions and 30 with continuous infusion) undergoing BMT. The influence of cyclosporin exposure on the probabilities of GVHD (grade > 0) and GVHD in skin, liver and intestine (score > 0) were assessed by binary logistic regression (R software).

Results

Patients characteristics are summarized in **table I**. Binary logistic regression found no significant link between blood cyclosporin AUC and the occurrence of GVHD. Conversely, there were significant links between AUCs in bone (including bone marrow) or thymus at the beginning of the treatment (0-24h) and the occurrence of GVHD ($p < 0.05$ in each case). Likewise, AUCs in skin and intestine (0-12h) were significant covariates of cutaneous GVHD and intestinal GVHD, respectively **(table II)**.

Table I. Patients characteristics

n	61
Median age (range), years	6.72 (0.5-17)
Median body weight (range), kg	21.1 (5.6-63)
Sex (% male)	54.5
Disease (%)	
Acute lymphoblastic leukemia	26.2
Acute myeloid leukemia	27.9
Other malignant hematological diseases	13.1
Non malignant haematological diseases	31.2
Metabolic diseases	1.6
Donor type (%)	
Related	52.5
Unrelated	47.5
aGvHD (n)	
Total aGvHD	34
Cutaneous aGvHD	32
Digestive aGvHD	7
Hepatic aGvHD	6
Infusion type (n)	
Intermittent	31
Continuous	30

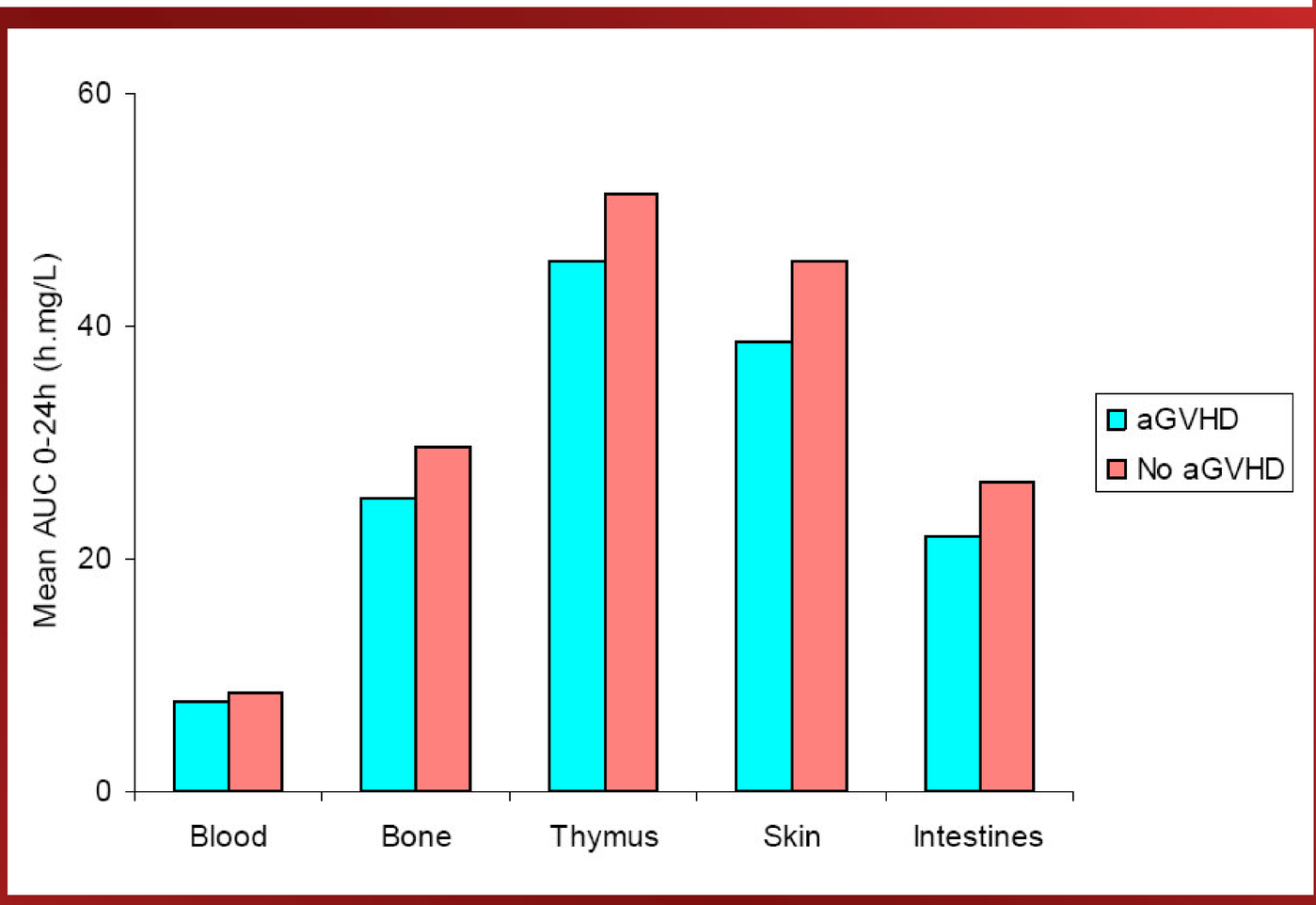

Fig. 1. Comparison of mean AUC (0-24 h) between GVHD and no GVHD

The ratio of mean AUCs (no aGVHD / aGVHD) was 1.18, 1.13, 1.18 and 1.21 for bone, thymus, skin and intestine, respectively **(fig. 1.).** Cyclosporin infusion duration was not a significant covariate of the occurrence of GVHD once AUCs were taken into account.

Table II. Binary logistic regression. Logit (Probability of aGVHD) = a0 + a1*AUC, p value for a1 = 0

		Probability	*a0*	*a1*	*p value (a1)*
Normalized AUC (0-24 h)	Blood	aGVHD	1,44	-1,16	0,23
	Bone		2,47	-2,07	<0.05
	Thymus		4,02	-3,60	<0.05
	Intestines		4,55	-4,06	<0.05
	Skin	Cutaneous aGVHD	2,20	-1,99	<0.05

Conclusion

In BMT, cyclosporin exposure in blood on day 1 was not a predictor of GVHD occurrence contrary to exposures in bone and thymus, which show the interest of the PBPK model. Differences in the pattern of GVHD depend only on differences in drug exposure in target tissues and not of duration of infusion per se. Non-linearity in tissue distribution explain these differences. The strong influence of cyclosporin exposure at day 1 confirms the importance of decreasing the activation of T-cells from the graft.