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LETTER TO THE EDITOR

Decreased insulin secretion in patients receiving tacrolimus as GVHD prophylaxis after allogeneic hematopoietic SCT

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As it has been reported that hyperglycemia is associated with a higher risk of non-relapse mortality after allogeneic hematopoietic SCT (HSCT), the efficient control of hyperglycemia has become an important consideration for safer HSCT.[1–3] A characteristic feature of this field is the use of calcineurin inhibitors, including tacrolimus (TAC), which may cause hyperglycemia as suggested in organ transplant settings, possibly by decreasing insulin secretion.[4] To evaluate this possibility, we serially monitored fasting glucose levels and serum immunoreactive insulin, and calculated homeostasis model assessment (HOMA)-IR and HOMA-β with the HOMA model[5] as recommended by Wallace *et al.*[6] HOMA-IR reflects insulin resistance and HOMA-β reflects the insulin secretion status.[5] If HOMA-IR increased after the administration of allogeneic HSCT, drugs that reduce insulin resistance, such as metformin or pioglitazone, might theoretically be effective. In contrast, if HOMA-β decreased, drugs that increase insulin secretion, such as glucagon-like peptide-1 analog or sulfonylureas, might be effective. The data from this study may help us to better understand how we should control glucose levels after HSCT.

Data obtained from 43 adult patients who received allogeneic HSCT from October 2006 to December 2007 were included in the analysis. The median age of the patients was 48 years (range: 19–66 years). When patients were not receiving s.c. long-acting insulin, systemic corticosteroid or parenteral nutrition, blood samples were obtained 1–2 months after HSCT. GVHD prophylaxis was started using CsA-based ($n=13$) or TAC-based regimens ($n=30$), with an additional short course of MTX in 35 patients. At the time of subsequent blood sampling, 15 patients were receiving CsA and 28 patients were receiving TAC, with no significant difference in various factors including age, gender, disease and intensity of the conditioning regimen (conventional vs reduced intensity), except that the TAC group included more HSCT with unrelated BM than the CsA group (89 vs 27%, respectively). The results regarding fasting glucose level, immunoreactive insulin and the HOMA model are summarized in Table 1.

We found that HOMA-β was significantly reduced in the TAC group compared with that in the CsA group, which was consistent with earlier studies in an organ transplant setting.[4] Clinically, it has been reported that GVHD prophylaxis with TAC is generally associated with a reduced incidence of acute GVHD compared with CsA. In contrast, hyperglycemia was associated with a higher risk of non-relapse mortality after allogeneic HSCT.[1,3] In our earlier study, patients with severe hyperglycemia had a significantly higher incidence of acute GVHD compared with normoglycemic patients.[3] Therefore, it is possible that hyperglycemia related to the use of TAC could offset the potential benefit of TAC, and drugs that increase insulin secretion, including the glucagon-like peptide-1 analog, may reverse the suppression of the insulin level.[7] Whether intensive glucose control could reduce the risk of acute

Table 1 Pretransplant and posttransplant glycemic status

Variable	N *(%)/ Median (range)*			
	Tacrolimus (n = *28*)		*CsA* (n = *15*)	
Fasting glucose level (mg per 100 ml)				
Pretransplant	87 (80–129)	$P=0.08$	89 (79–154)	$P=0.55$
Posttransplant	95 (79–129)		91 (80–116)	
Immunoreactive insulin level (μU/ml)				
Pretransplant	6.1 (1.6–17.3)	$P=0.60$	6.6 (2.9–13.5)	$P=0.25$
Posttransplant	6.5 (1.5–18.0)		5.3 (2.4–10.1)	
HOMA-IR				
Pretransplant	1.4 (0.3–4.6)	$P=0.75$	1.4 (0.6–5.13)	$P=0.40$
Posttransplant	1.5 (0.3–4.2)		1.3 (0.5–2.2)	
HOMA-β				
Pretransplant	90.9 (30.3–193.7)	$P=0.04$	65.4 (38.7–160.0)	$P=0.43$
Posttransplant	69.9 (15.8–202.5)		61.7 (28.5–180.0)	

Abbreviations: HOMA = homeostasis model assessment; IR = insulin resistance.

GVHD in patients using TAC should be evaluated by prospective randomized control trials.

In conclusion, this is the first study to assess the change in the glycemic status with the HOMA model in patients undergoing HSCT with CsA or TAC. We showed that GVHD prophylaxis with TAC was associated with decreased insulin secretion and a resultant tendency for hyperglycemia. It is possible that measures to keep insulin and glucose levels within their respective normal ranges are effective for reducing morbidity and mortality after HSCT.

Conflict of interest

The authors declare no conflict of interest.

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S Fuji[1], S-W Kim[1], S Mori[1], K Furuta[2], R Tanosaki[1], Y Heike[1], Y Takaue[1] and T Fukuda[1]

[1]*Division of Stem Cell Transplantation, National Cancer Center Hospital, Tokyo, Japan and*

[2]*Division of Laboratory Medicine, National Cancer Center Hospital, Tokyo, Japan*

E-mail: tafukuda@ncc.go.jp

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