Abnormalities of GPIb and GPIIb/IIIa Platelet Surface Glycoproteins in Adult and Paediatric Renal Transplant Patients

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Dear Sir,

A major problem in transplanted patients under immunosuppressive therapy is ciclosporin toxicity. Ciclosporin induces microvascular and endothelial damage: in renal allografts platelet-fibrin aggregates are frequently seen during the first weeks after transplantation, and there is an increased incidence of arterial and venous thromboses [1, 2]. Platelet hyperaggregability is easily demonstrated together with an increase of the plasma von Willebrand factor (vWF) concentration, a marker of endothelial injury. Recently important alterations of platelet surface receptors in renal transplant patients under ciclosporin therapy have been described [3]. The platelet surface glycoprotein GPIb, the receptor for vWF, and GPIIb/IIIa, the receptor for fibrinogen, are closely related to the mechanism of platelet adhesion and aggregation and play an important role in platelet-endothelium interactions. When the damaged subendothelial matrix, which contains a large amount of vWF multimers, is exposed to flowing blood, platelets initially adhere through the interaction between vWF and platelet surface glycoprotein GPIb and subsequently between vWF and glycoprotein GPIIb/IIIa. Platelet aggregation is mediated by fibrinogen which links two adjacent platelets through glycoprotein GPIIb/IIIa. Recent reports demonstrated the importance of glycoproteins GPIb and GPIIb/IIIa in haemostatic balance and thrombotic phenomena, and their expression (reduced or increased) has been well correlated with clinical events in uraemic platelet disorders, in erythropoietin-induced hypertension and thrombosis, and in polyunsaturated fatty acid (omega 3 fish oil) induced antiaggregation (a possible index of ciclosporin nephro-toxicity), in renal transplant patients. There are two well-defined platelet disorders in which a deficiency of platelet surface

receptors plays an important role: in the Bernard-Soulier syndrome, a specific defect of GPIb glycoprotein is well correlated with a reduced platelet adhesion, and patients suffering from the Glanzmann thrombasthenia show a marked deficiency of GPIIb/IIIa glycoprotein, with a clearly reduced platelet aggregation.

Further, while an increase of expression of platelet surface glycoproteins can be correlated with a predisposition to atherosclerotic and thrombotic phenomena, a further contribution was given by the EPIC Study [4], in which a prevention of ischaemic complications in high-risk angioplasty by a monoclonal antibody c7E3 Fab against platelet GPIIb/IIIa receptor was clearly demonstrated.

The aim of this study was to investigate the abnormalities of platelet surface receptors in adult renal transplant patients in comparison to kidney-transplanted children,

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in order to establish whether the different immunological and hormonal background in these different groups of patients could be involved in the different susceptibility to ciclosporin toxicity.

Platelet surface receptors GPIb and GPIIb/IIIa were investigated with monoclonal antibodies CD42 and CD41 (Immu-notech) and a Facscan flow cytometer (Becton Dickinson).

The mean GPIb glycoprotein values (mean flow $\pm$ SD) in adult renal transplant patients treated with ciclosporin (n = 13) were 61.69 ± 11.27 and in normal subjects (n = 10) 48.43 ± 9.96 (p < 0.001); the mean values in kidney-transplanted children (n = 6) were 33.66 ± 11.32 and in healthy children (n = 6) 42.69 ± 12.75 (p = NS). The

mean values of GPIIb/IIIa glycoprotein in adult renal transplant patients were 537.59 ± 91.87 and in normal healthy controls 382.26 ± 97 (p < 0.001); the mean values in kidney-transplanted children were 418.75 ± 25 and in healthy children 370.64 ± 45 (p < 0.025).

Our data suggest that the alterations of platelet-endothelium interactions, mediated by an increase in the expression of platelet surface glycoproteins GPIb and GPIIb/IIIa, may play a role in ciclosporin nephrotoxicity.

In the paediatric renal transplant population these abnormalities are less marked: the prepubertal hormonal subset could be involved in a different susceptibility to ciclosporin-induced damage.

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