Endothelin-1 Receptor Blockade and its Effect on Chronic Rejection


Endothelin-1 (ET-1), a 21 amino acid peptide with potent vasoconstrictive properties has been implicated in the development of acute allograft rejection.\(^1\) It is primarily produced by endothelial cells and its secretion, during acute rejection episodes, has been shown to be upregulated by TGFβ and other proinflammatory cytokines released by graft infiltrating cells.\(^3\) Additionally, ET-1 has also been shown to facilitate proliferation of α-smooth muscle actin-positive (α-smA\(^+\)) cells.\(^2\) Given that proliferation and/or accumulation of α-smA\(^+\) cells is a prominent feature in neointimal thickening encountered in posttransplant vasculopathy, it is rational to propose that ET-1 may play an important role in the pathogenesis of this lesion. To test this tenet, we proceeded to block ET-receptors (both ETA and ET\(_B\)) by bosentan (a non peptide antagonist of ET-1) and to study its influence on the evolvement of chronic rejection (CR) in an established mouse model of aortic allotransplantation.\(^3\)

MATERIAL AND METHODS

Animals/Aortic Transplantation (Tx)

Aortic grafts were transplanted across major histocompatibility complex-disparate C57Bl/10 (H\(^2b\)) → C3H (H\(^2k\)) mouse strain combination and harvested at day 30 postimplantation for morphologic and immunohistochemical analysis. While controls (n = 6) received PBS only, those in the study (n = 6) group were treated daily with bosentan (100 μg/animal; iv; kindly provided by Dr Brian Bryzinsky, Hoffman-LaRoche, Nutley, NJ) until allograft harvest.

In Vitro Analysis

The titer of donor-specific alloantibodies was determined by microcytotoxicity assay. Additionally, plasma ET-1 levels were also ascertained by enzyme-linked immunosorbent assay (Peninsula Lab, Inc, Belmont, Calif). For these tests, recipient plasma was obtained at the time of allograft harvest (~day 30 post-Tx).

RESULTS AND DISCUSSION

Histopathologic examination of aorta harvested from animals treated with PBS alone revealed marked intimal thickening due to proliferation of α-smA\(^+\) cells. Additionally, there was a variable degree of disruption of the internal elastic membrane with adventitial but not intimal, mononuclear cell infiltration. On the contrary, allografts harvested from the majority of the animals treated with bosentan exhibited marked reduction in morphologic aberrations as compared to that to controls. These findings are consistent with earlier observations that also demonstrated that the use of an ET-1 receptor antagonist (SB 209670) mitigated neointimal formation in a rat model of carotid artery balloon angioplasty.\(^4\) Interestingly, despite attenuation of morphologic aberrations, animals treated with bosentan had comparable titers of anti-donor humoral responses as compared to that to controls. This finding supports our earlier contention\(^5\) that the prevailing notion underscoring the seminal role of alloantibodies in the pathogenesis of CR needs careful reconsideration. Taken together, these data suggest that ET-1 plays an important role in the pathogenesis of posttransplant vasculopathy and, therefore, its blockade by the use of exogenous agents may have significant clinical utility.

REFERENCES


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