Characterization of in vivo Prostacyclin Biosynthesis in Patients with Essential Thrombocytemia and Effects of Different Aspirin Regimens

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Essential Thrombocythemia (ET) is a myeloproliferative neoplasm (MPN) characterized by high platelet generation and thrombotic diathesis requiring antithrombotic prophylaxis. Once daily (od), low-dose aspirin is commonly recommended on the basis of one clinical trial in patients with a different MPN. However, it has been recently shown that od, low-dose aspirin is unable to fully inhibit platelet-derived thromboxane (TX)A_2. A twice daily dosing regimen is necessary to lower TXA_2 to levels comparable to non-ET subjects on low-dose aspirin. However, shortening the aspirin dosing interval might affect in vivo vascular PGI_2 biosynthesis. To characterize in vivo PGI_2 biosynthesis in ET patients treated with 100 mg od enteric coated (ec) aspirin and to determine whether increasing the daily dose (200 mg od) or frequency of dosing (100 mg twice daily, bid) can lower in vivo PGI_2 synthesis. PGI_2 biosynthesis was assessed by measurement of its urinary metabolite 2,3-dinor-6-keto-$PGF_{1\alpha}$ (PGI-M). In a cross-sectional study the determinants of PGI-M biosynthesis were characterized in 50 ET patients. In a crossover study 22 ET patients were randomized to different sequences of the following regimens: 100 mg od, 100 mg bid, 200 mg od ec aspirin or plain aspirin 100 mg od. The latter patients had serum TXB_2 levels ≥ 4 ng/ml on standard treatment. By multiple regression analysis on the entire cohort of 50 patients, urinary PGI-M was inversely associated with disease duration (p=0.013), platelet distribution width (p=0.005) and directly correlated with female sex (p=0.027) and urinary 11-dehydro-TXB_2 (p=0.019). Considering the subgroup of 22 patients, PGI-M and CRP were inversely correlated (p=0.019). Neither twice daily 100 mg (203.4 pg/mg creatinine [145.8-308.2], median [IQR] values) nor 200 mg od (188.1 [154.1-251.7]) significantly modified in vivo PGI_2 biosynthesis, as compared to the standard regimen (p=0.43; p=0.31, respectively). PGI-M levels were also similar in 100 mg od ec aspirin and in plain aspirin 100 mg od (p=0.21). In ET patients female sex, indexes of platelet immaturity, and disease duration appear to influence vascular PGI_2 production. A twice daily low-dose aspirin regimen does not appear to affect in vivo PGI_2 biosynthesis, thus providing a rationale for testing its clinical efficacy and safety on ET.