POOR RESPONSIVENESS TO LOW-DOSE ASPIRIN IN POLYCYTHEMIA VERA PREDICTS RESIDUAL IN VIVO PLATELET ACTIVATION

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Polycytemia Vera (PV) is a myeloproliferative neoplasm characterized by erythrocytosis, panmyelosis and increased thrombotic risk impacting on morbidity and mortality. Low-dose aspirin (ASA) once-daily (od) is recommended for both secondary and primary cardiovascular prevention in PV, mainly based on the results of the ECLAP trial, which randomized low-dose ASA vs. placebo in PV patients without a clear indication to ASA, with ≈70% of the patients in primary prevention. This trial was terminated early due to slow recruitment, failed to show a significant benefit of ASA on the combined the primary endpoint of nonfatal myocardial infarction, stroke, or cardiovascular death, while it showed a significant benefit when this primary endpoint was combined with non-fatal venous thromboembolism. Moreover, current guidelines suggest 100mg ASA twice-daily for PV patients at high cardiovascular risk, defined by JAK2V617F positivity or age >60 years, on the assumption of a need of an intensified antiplatelet regimen, without supporting evidence. Thus, the pharmacodynamics of od low-dose ASA would need further investigation in PV.

Objectives. To study the responsiveness to standard ASA (100 mg od) in patients with PV, assessed at the end of the dosing interval.

Methods. Patients were asked to take ASA always at 8 am, blood and urine samples were collected 24 h after the last ASA intake on a fasting state. Routine hematochemistry, genotyping, clinical characteristics and medications were recorded. In addition we also measured: serum thromboxane (TX)B2 as the ex vivo biomarker of ASA pharmacodynamics, urinary 11-deidro-TXB2 (TXM) as an in vivo index of platelet activation, the major urinary prostacyclin metabolite, the 2,3 dinor 6-keto-PGF1α (PGIM), the urinary isoprostane 8-iso PGF2a and the plasma esterase activity on ASA.

Results. We studied 47 PV patients (mean age 67±10 years, 15 females) all on low-dose ASA (100mg/od) for ≥1 month, according to current guidelines. Thirty-seven patients were on hydroxyurea alone or combined with phlebotomies (n=23), 9 patients were on phlebotomies only, to keep hematocrit <45%. Average haematologic values were: haematocrit 44±3%; erythrocytes 5.1±1.5x109/uL; leukocytes 9.1±4.4x103/uL, platelets 355±156x103/uL, immature platelets 12.1±7.6x103/uL. Median sTXB2 value was 9 [4-16] ng/ml, urinary TXM 483 [341-710] pg/mg creatinine, 8-iso 744 [549-1042] pg/mg creatinine, PGIM 172 [120-275] pg/mg creatinine, plasma esterase activity 53 [47-60] µmol/L SA/min. Serum TXB2 and TXM 24 hours after ASA intake were significantly higher than the values in previously-published healthy controls ($p<0.019$). sTXB2 significantly ($p<0.05$) correlated with immature platelets (rho=0.42), erythrocyte count (rho=0.39), polymorphonucleates (rho=0.36). Multiple regression analysis showed only a trend for immature platelets ($p=0.08$) in predicting sTXB2. Urinary TXM significantly ($p<0.05$) correlated with sTXB2

(rho=0.38 and Figure), disease duration (rho=0.32), previous thrombosis (rho=0.31), leukocytes (rho=0.32). By multivariable analysis, previous thrombosis (p=0.02) and sTXB2 (p=0.004) positively predicted urinary TXM excretion. PGIM correlated with 8-iso PGF2a excretion but not with TXM. Plasma esterase activity on ASA positively correlated with haemoglobin levels (rho=0.33, p=0.04), but not with haematocrit, erythrocyte count, TXM or sTXB2. JAK2V617F allelic burden was significantly associated with age (rho=0.5) and polymorphonuclear (rho=0.66) counts while it was unrelated to previous thrombosis, sTXB2, TXM, PGIM, and it was an independent predictor of polymorphonuclear counts (p<0.001).

Conclusions. Polycythemia Vera appears to have a reduced response to standard low-dose ASA, at least in a fraction of patients. High residual sTXB2 contributes to the enhanced in vivo platelet activation observed in this disorder. Thus, a more intensive antiplatelet regimen might be tested in these patients.

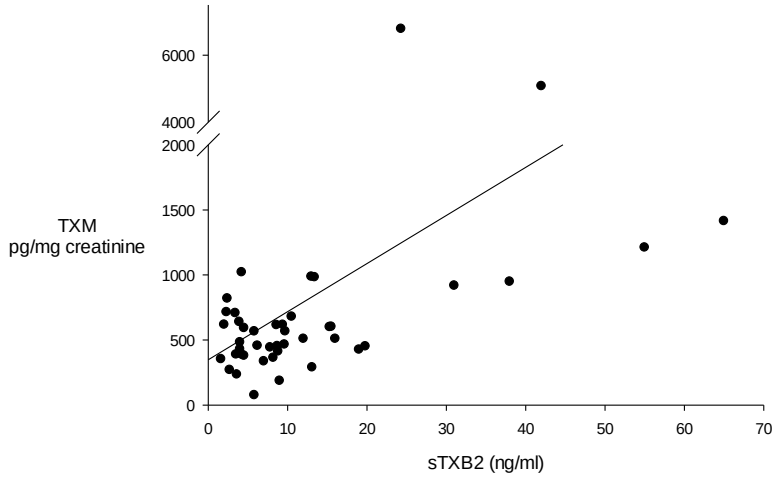

Figure. Correlation between sTXB2 and TXM values in 47 PV patients.