Clopidogrel treatment suppresses ADP-dependent platelet activation but associates with worsening of markers of endothelial dysfunction and development of new digital ulcers in patients with systemic sclerosis.

AA 002

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Introduction: Data indicate that activated platelets release serotonin that binds 5-HT_{2B} receptor on fibroblasts leading to fibroblast activation[1]. Clopidogrel, an inhibitor of the P2Y12 ADP receptor, was shown to prevent fibrosis in several animal models of SSc[2].

Endothelial Activation

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Platelet Activation

↓

Serotonin Release

↓

Fibroblast Activation

↓

Fibrosis

Objective: To assess the effect of clopidogrel treatment in patients with SSc on i) ADP-dependent platelet activation, ii)plasma serotonin levels and iii) clinical outcomes

Methods: We recruited 14 patients with SSc and 8 patients with rheumatoid arthritis as controls. Platelet activation was assessed by Multiplate (Roche), prior to and following 10 days of clopidogrel treatment (75 mg daily). At the same time points serotonin was measured in platelet poor plasma by RIA and endothelial markers (s-ICAM and s-VCAM) by ELISA.

Figure 1

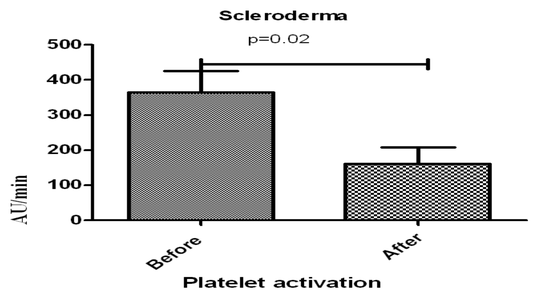


Figure 2

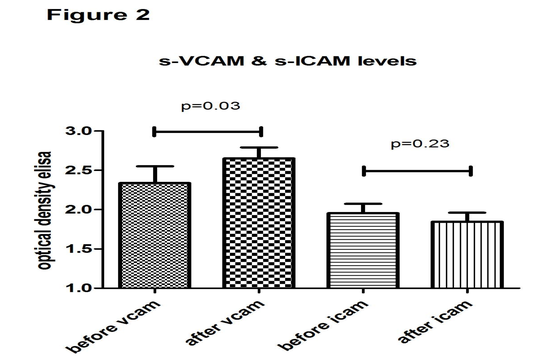
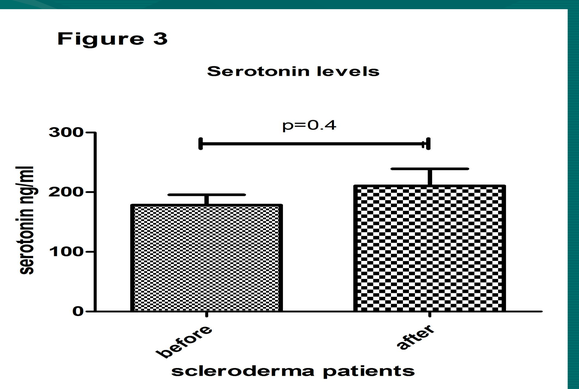


Figure 3



Conclusion: Clopidogrel may worsen markers of endothelial function and associate with development of new digital ulcers in patients with SSc.

Results: Most patients with SSc were female (n=13), had limited disease (n=11) with a mean age of 63.5 and disease duration of 11 years. Platelets were highly activated in patients with SSc with 6 patients (42.8%) showing high platelet reactivity (>468 AU/min) in sharp contrast to only 1 patient (12.5%) in the RA group. Clopidogrel treatment significantly reduced platelet reactivity in patients with SSc (mean±SEM AU/min:364.9±60.5 vs 160.6±47.9, prior to and following treatment respectively, p=0.02) but not in patients with RA (p=0.5). Plasma serotonin levels did not change following treatment (mean±SEM ng/ml:182±16 vs 206±26, p=0.4). Indices of internal organ function (PFTs, eGFR, RVSP) remained stable. s-ICAM levels did not change but s-VCAM increased (p=0.03) following clopidogrel treatment. **Three patients developed digital ulcers: 1) patient with early, progressive disease, 2) patient with late disease and history of digital ulcers but with no ulcers during the last 8 years while on bosentan and most strikingly 3) patient with disease duration of 15 years and no history of digital ulcers.**

Reference: 1)Dees et al.2011
2)Iwamoto and Distler 2012