Biomarker Profiling of Patients with Polycythemia Vera Relative to Healthy Subjects: Baseline Characteristics of Patients Enrolled in the PACIFIC Study

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Introduction

- Polycythemia Vera (PV) is a stem-cell-derived chronic myeloproliferative neoplasm (MPN) characterized by erythrocytosis, often associated with leukocytosis and thrombocytosis. Polycythemia vera (PV) is defined by an acquired increase in hemoglobin (Hb)/hematocrit (HCT), associated with increased blood viscosity, cardiovascular/thrombotic events and iron deficiency.[1] Most patients with PV are iron deficient and therapeutic phlebotomy may exacerbate iron deficiency.[2]
- Rusfertide, a subcutaneously administered peptide, is a hepcidin mimetic that has been shown to control erythrocytosis in patients with PV.[3]
- The Phase 2 PACIFIC study (PTG-300-08; clinicaltrials.gov NCT04767802) was an open-label, 52-week, phase 2 study that investigated the efficacy and safety of rusfertide in 20 Asian subjects with poor hematocrit (HCT) control as noted by HCT >48%.

Objectives

To understand changes in the biomarker profile in patients with PV relative to healthy subjects and to characterize the correlation between biomarkers.

Methods

The PACIFIC study enrolled 20 patients with PV in Malaysia and S. Korea who had hematocrit >48% at study entry. Almost all patients (18/20) were on prestudy hydroxyurea.
Serum samples collected at baseline from patients were used to measure biomarkers using multiplex panels (Rules-Based Medicine, TX, USA) and by ELISA. Serum samples from healthy subjects (N=12-48) served as controls. Biomarkers were summarized by hierarchical clustering using the Interactive Clustered Heat Map Builder.[4] Significant correlations (r^2>|0.7|, p<0.05) among biomarkers were identified using Pearson's correlation.

Results

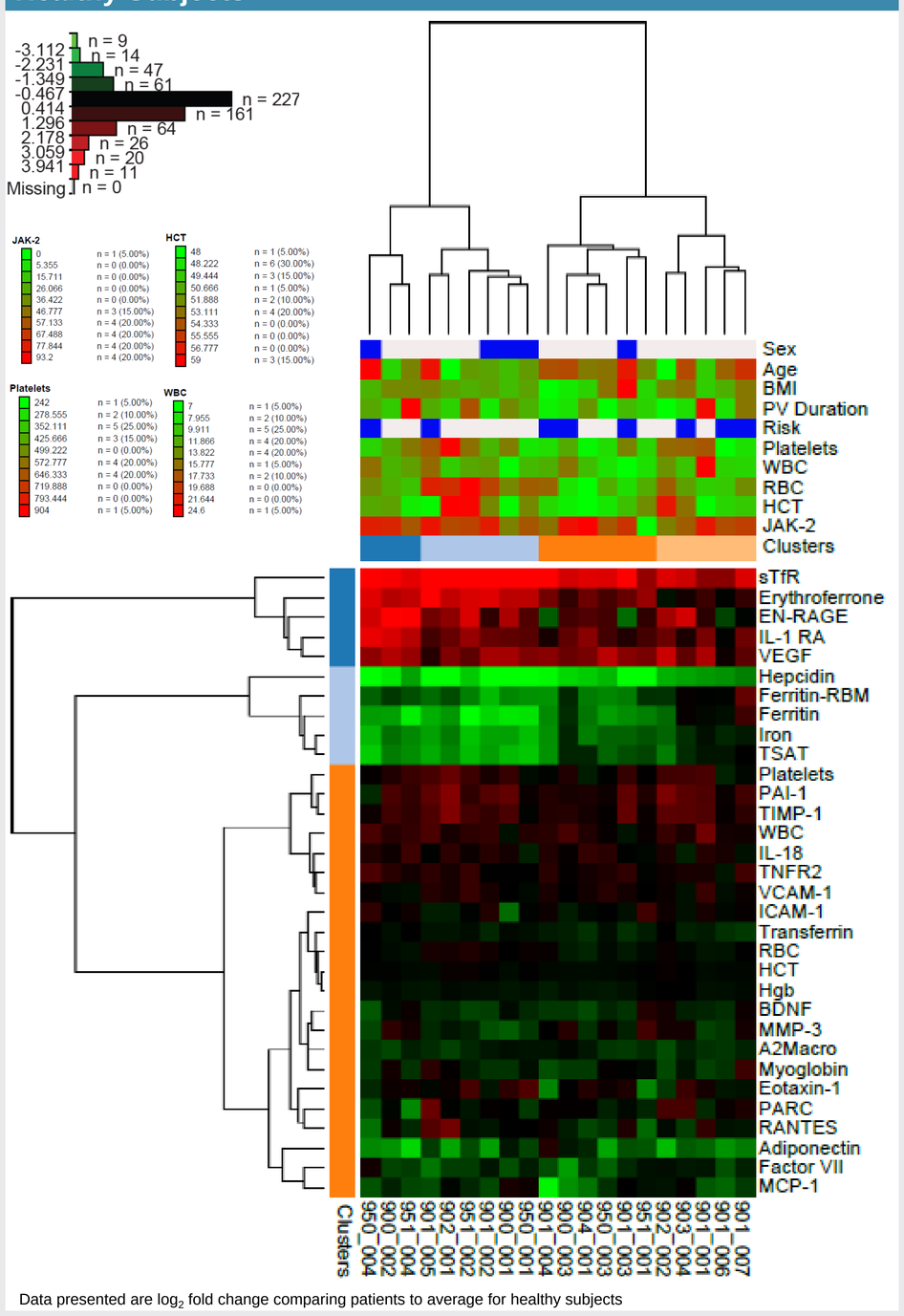
- Demographics and baseline characteristics are presented in Table 1

Table 1. Demographics and Baseline Characteristics

Category	n (%)
Age	
≤ 60	13 (65.0)
Sex	
Male	15 (75.0)
PV Duration (years)	
≤ 1	3 (15.0)
>1 - ≤ 5	11 (55.0)
>5	6 (30.0)
Risk Category	
High Risk: Age[1]	8 (40.0)
Low Risk	12 (60.0)

[1] No patients were High Risk due to prior history of thromboembolic events

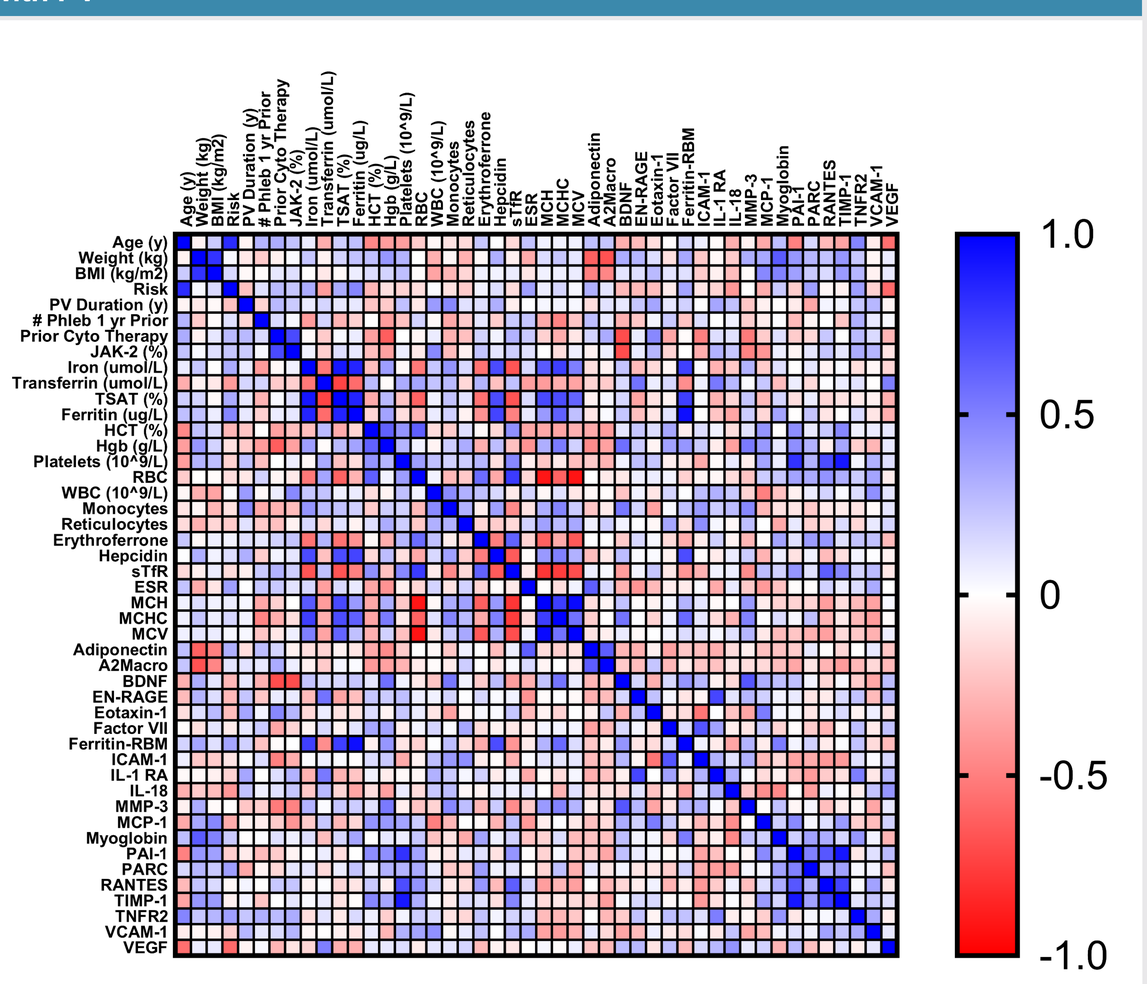
Figure 1a. Comparison of Biomarkers in Patients with PV and Healthy Subjects



Data presented are $\log_2$ fold change comparing patients to average for healthy subjects

- Serum levels of various biomarkers, including several proinflammatory cytokines, were significantly higher at baseline in patients with PV compared to healthy subjects (Figure 1a).
- sTfR, erythroferrone, EN-RAGE, IL 1RA and VEGF were upregulated (cluster 1), hepcidin, ferritin, iron, and adiponectin were downregulated in patient with PV relative to healthy subjects.
- IL-18, IL-1RA, TIMP-1, PAI-1, VCAM-1, and VEGF were significantly higher (p≤0.001) in patients compared to healthy subjects.
- EN-RAGE, Eotaxin-1, ICAM-1, PARC, and RANTES, were higher in patients compared to healthy subjects (p<0.05).
- Hepcidin was significantly lower (p<0.001), and adiponectin was lower in PV patients compared to healthy subjects. Erythropoietin was detectable in 4/20 (20%) PV patients and in 9/12 (75%) healthy subjects.
- Levels of interferon gamma, IL-1α, IL-1β, IL-2, IL-3, IL-5, IL-7, IL-10, IL-12p70, IL 17, and TNF-β were below the limit of detection in both patients and healthy subjects.
- IL-4, IL-6, IL-8, and IL-12p40 were detected in 2/20 (10%), 0/20, 6/20 (30%), and 6/20 (30%) PV patients and in 1/48 (2%), 1/48 (2%), 8/48 (17%), and 44/48 (92%) healthy subjects, respectively.
- MIP-1α, MMP-9, and TNF-α were detectable in 3/20 (15%), 0/20, and 2/20 (10%) PV patients and in 4/48 (8%), 2/28 (4%), and 0/48 healthy subjects, respectively.
- Strong positive correlations were noted between age and risk; between JAK-2 burden and prior cytoreductive therapy; between iron and TSAT, ferritin, hepcidin, MCHC; between TSAT and ferritin, MCH and MCHC; between ferritin and hepcidin; between platelet count and PAI-1, TIMP-1; between erythrocyte count and sTfR; between EN-RAGE and IL-1 RA, and between TIMP-1 and PAI-1, RANTES (Figure 1b).
- Strong negative correlations were noted between JAK2 burden and BDNF; between transferrin and TSAT; between erythrocyte count and MCH, MCV; and between sTfR and MCH, MCHC.

Figure 1b. Correlation of Biomarkers and Baseline Characteristics in Patient with PV



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Conclusion

- The biomarker profile in PV patients with high hematocrit levels relative to healthy subjects appears distinct from other MPNs
- Additional studies are needed to understand the clinical relevance and effect of therapeutic intervention on these biomarkers in patients with PV.