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A remarkable hematological and molecular response pattern in a patient with polycythemia vera during combination therapy with simvastatin and alendronate



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ABSTRACT

We report a 57-year old man with polycythemia vera, who had a remarkable hematological and molecular response during treatment with simvastatin and alendronate. The patient was treated with this combination for 56 months, and during this period the patient has been in complete hematological remission. The JAK2-V617F allele burden has dropped from 64% to sustained values below 20%, and follow-up bone marrow biopsies have revealed no change in PV features, without any regular cytoreductive treatment.

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1. Case report

In 2008 a 57-year old man was referred for treatment of polycythemia vera (PV). One year earlier he had been admitted with symptoms resembling an episode of transitory cerebral ischemia (TCI). The patient also had a history of multiple sclerosis (MS), vitamin B12 deficiency and tobacco smoking. The MS was not being treated at this point and the B12 deficiency was treated with cyanocobalamin 1 mg/day. At that time the hemoglobin concentration (Hgb) was elevated at 18.5 g/dL, the hematocrit (HCT) was 54%, and the white blood cell count (WBC) was $11.0 \times 10^9/L$. The platelet count was $502 \times 10^9/L$. Mean corpuscular volume (MCV) was normal 97 fL. A cerebral CT-scan showed a hypodense area compatible with an infarction of indeterminable age. The patient was treated with acetylsalicylic acid 75 mg/day, dipyridamole 200 mg 2 times/day along with simvastatin 40 mg/day. The patient was phlebotomized once before discharge. Unfortunately, although the elevated blood cells should have raised the suspicion of PV, the patient was not referred to a department of hematology, and no JAK2-V617F mutation analysis was done at this time.

The patient was referred to the department of hematology in

2008 by his general practitioner because of sustained elevated Hgb-concentrations and platelet counts along with fatigue. At the time of the PV diagnosis the Hgb concentration was 19.2 g/dL and the HCT 0.60. The WBC was $12.0 \times 10^9/L$, and the platelet count $485 \times 10^9/L$, the MCV 91 fL and B12 vitamin was elevated at 882 pmol/l. MCV remained normal and B12 normal or elevated. The red cell mass and plasma volume were both expanded, and serum-EPO was lowered at 1 IU/L. The JAK2-V617F mutation was positive with an allele burden of 64%. A bone marrow biopsy was compatible with PV with a slightly hypercellular bone marrow with panmyelosis and depleted iron stores, displaying no reticulin fibrosis and a peripheral blood-smear was without leucoerythroblastosis. Immunohistochemical staining with CD34 showed dilated vessels, but no increase in vascular density. An abdominal ultrasound showed normal spleen size. Based on the above findings the diagnosis PV was made.

During the following year 11 phlebotomies were performed and no cytoreductive treatment was administered. Fig. 1 illustrates the treatment and responses in hematological parameters along with the JAK2-V617F allele burden. Approximately 13 months after the PV-diagnosis, treatment with hydroxyurea (HU) 500 mg/day was initiated in order to reduce the need of phlebotomies and to normalize elevated leukocyte and platelet counts. Eighteen days later the patient was admitted to a department of neurology with convulsions and fever, being suspected of an attack of MS. Clinically a pneumonia was suspected, and a chest x-ray revealed

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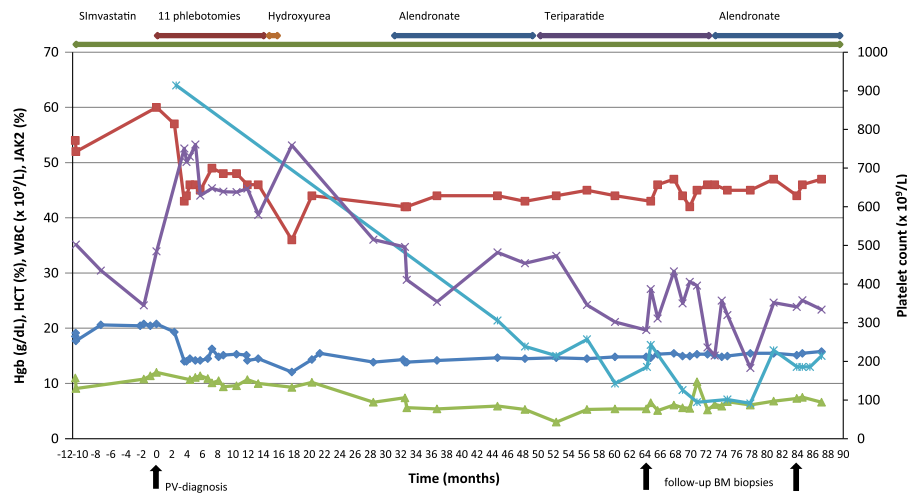


Fig. 1. The development of hematological parameters and the JAK2-V617F allele burden and an overview of the treatment.

multiple pulmonary infiltrates. Accordingly, treatment with antibiotics was initiated. No bacterial growth from blood, urine or sputum was recorded. After 3 days of admission HU was discontinued. Later, the patient developed shock and was transferred to the intensive care unit. A CT-scan of the chest and abdomen revealed signs of pulmonary alveolitis. A bronchoscopy was normal. No biopsy was performed. It was concluded that the alveolitis likely was induced by HU, since the patient steadily improved after HU was discontinued.

At follow-up in the hematological out-patient clinic the patient had a normal HCT and the platelet count was slightly elevated at $515 \times 10^9/L$. However, no further cytoreductive treatment was

initiated. At the beginning of 2011 (31 months after the PV-diagnosis) osteoporosis was diagnosed. Consequently, treatment with alendronate 70 mg/week was initiated and continued for 18 months, until the patient changed treatment to Teriparatide – a PTH analog – for two years. Afterwards alendronate was re-introduced. During these 56 months, after initiation of alendronate, the patient was largely in complete hematological remission (the platelet count was temporarily above $400 \times 10^9/L$ on some occasions) without need for further phlebotomies, and the JAK2-V617F mutation status 44 months after PV-diagnosis revealed a marked decrease in the allele burden from 64.0% to 21.4% (Fig. 1). The patient had no need of phlebotomies or cytoreductive

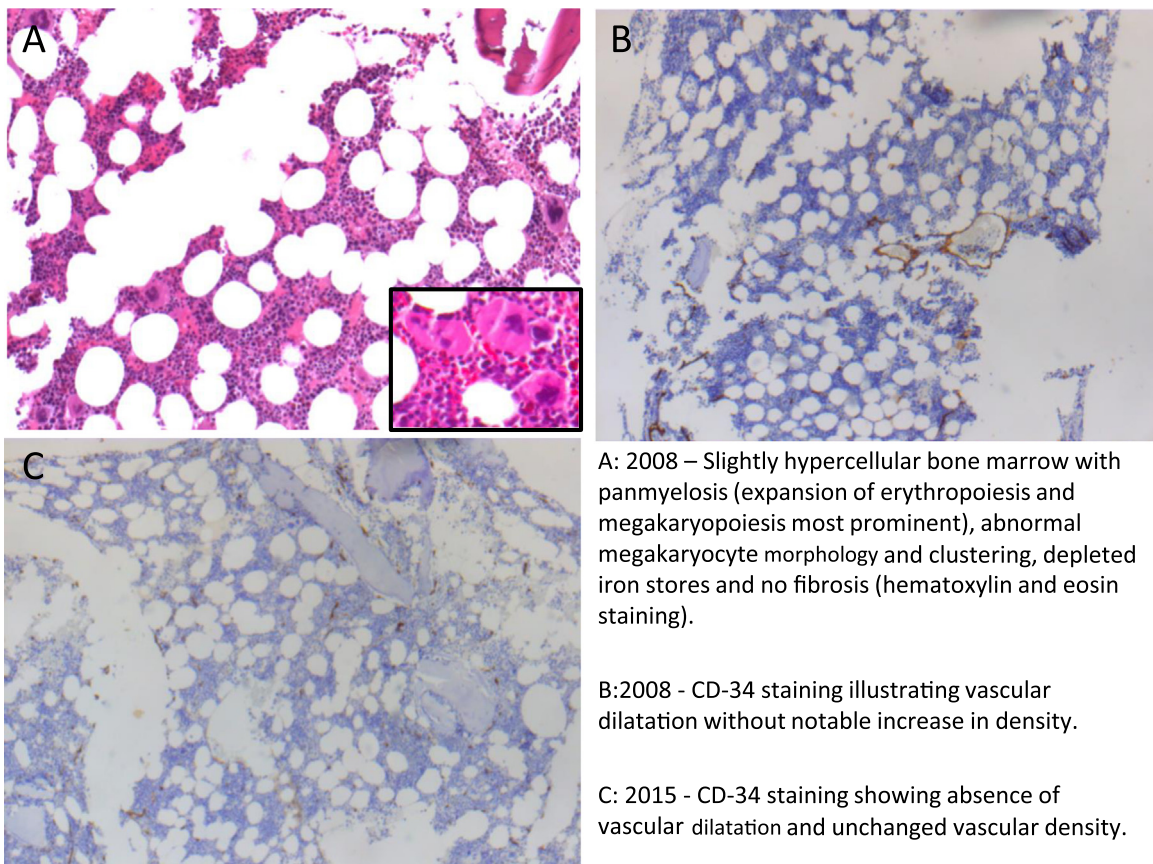


Fig. 2. Bone marrow biopsies from 2008, 2013 and 2015.

treatment to reduce elevated cell counts, and no thrombohemorrhagic events occurred. Subsequent serial measurements of the JAK2-V617F allele burden have shown sustained values below 20% and even below 10% on some occasions. Two follow-up bone marrow biopsies at 33 and 53 months after institution of statin and bisphosphonate combination therapy (64 and 84 months after PV-diagnosis) displayed stable disease with remaining features of PV. Despite this, the vascular dilatation found in the initial bone marrow biopsy had disappeared in the two following biopsies (Fig. 2).

2. Discussion

This case report demonstrates for the first time a remarkable hematological and molecular response with a marked sustained decrease in the JAK2-V617F allele burden during statin and bisphosphonate combination therapy of a patient with PV. Both agents potentially inhibit the mevalonate pathway, which has been suggested as a therapeutic target in multiple cancer types [1] and also in the treatment of MPNs [2]. An association between chronic inflammation and the development and progression of MPNs has been proposed [3], and both statins and bisphosphonates possess potent anti-inflammatory, anti-neoplastic, anti-thrombotic and anti-angiogenic properties unrelated to the cholesterol lowering effects of statins [1,2,4]. These effects are probably mediated by inhibiting the synthesis of the important isoprenoid intermediates such as farnesylpyrophosphate (FPP) and geranylgeranylpyrophosphate (GGP). These intermediates are important in the post-translational modification of a variety of proteins. When activated these pathways induce increased cellular growth, proliferation, migration and oxidative stress. Accordingly, their inhibition might theoretically dampen inflammation and ultimately tumor development [1,4]. Importantly, simvastatin (and other statins) induce apoptosis and inhibit JAK2-V617F-dependent cell growth in MPN cell lines. Furthermore, the MPN-associated JAK2-V617F kinase localization to lipid rafts and its signaling is inhibited by statins [5]. Also, the pro-inflammatory cytokines TNF-alpha and IL-6 are decreased during statin treatment in a wide variety of inflammatory conditions [6], TNF-alpha being able to facilitate clonal expansion of JAK2-V617F-positive cells in MPNs [7]. Both statins and bisphosphonates inhibit the release of VEGF. VEGF mediated neo-angiogenesis may in part be responsible for the bone marrow fibrosis observed in myelofibrosis [1,2]. This effect may be observed in the bone marrow of this patient, where the CD34 staining revealed vascular dilatation in 2008 but not in the following two biopsies. Release of VEGF from the tumor cells may be responsible for the vascular dilatation observed [8].

Regarding the reduction in JAK2-V617F allele burden, the patient only received treatment with HU for 18 days during the initial disease course. Thus, it is reasonable to conclude, that the ensuing marked decrease in the JAK2-V617F allele burden over the first 44 months after the PV diagnosis was not related to HU-treatment. Although HU has been shown to reduce the JAK2-V617F allele burden in some studies, other studies have failed to reproduce this effect [9]. Importantly, the effect of HU on peripheral blood cell counts and the JAK2-V617F allele burden is but temporary with rising cell counts within a few days after HU being discontinued. We believe that the response is a result of the treatment with simvastatin and from month 31 the addition of alendronate. However, since 44 months elapsed between the first two JAK2-V617F analyses, we are unable to relate the decrease in the JAK2-V617F allele burden directly to the initiation of alendronate treatment. Interestingly, during the two years of teriparatide treatment, when alendronate was paused, the JAK2-V617F allele burden was relatively stable. The following

stabilization of the disease parameters might suggest that a long-term bisphosphonate treatment is redundant, and instead a short-term treatment plan with bisphosphonate followed by continuous statin treatment might be a better strategy. During this period the patient was treated with the platelet inhibitors ASA and dipyridamole. Dipyridamole is a phosphodiesterase inhibitor similar to anagrelide which is used in the treatment of essential thrombocytosis to reduce platelet count, but not in the standard treatment of PV [10]. Dipyridamole has been shown to inhibit the proliferation of peripheral blood mononuclear cells from patients with CML and AML in-vitro [11], and could have influenced the hematological response in this patient. On the other hand dipyridamole can also stimulate hematopoietic reconstitution in irradiated mice [12]. No studies have shown an effect on human blood cell counts in-vivo. Thus, we do not believe that dipyridamole is responsible for the remarkable response. Likewise, there is no evidence to suggest that ASA could have caused the response.

Prior case reports have described hematological remission in patients with myelofibrosis during treatment with bisphosphonates, but a phase II study investigating the effects of zoledronic acid on patients with myelofibrosis showed responses in only 1 of 16 patients [13].

In conclusion, we report complete hematological response in concert with a partial molecular response in a patient with PV treated with alendronate and simvastatin. Although bisphosphonate monotherapy – as illustrated by Delforge et al. [13] – may rarely be beneficial in the late myelofibrosis stage, the highly remarkable response in our patient on combination therapy with statin and bisphosphonate, possibly exhibiting different but synergistic blocking effects in the mevalonate pathway, is certainly an encouraging stimulus for further experimental and clinical research on the potential role of these “old drugs” in the treatment of MPNs alone or adjuvant to HU, interferon-2a or JAK1/2 inhibitors [3]. Furthermore, a greater response may be expected in the earlier stages of the MPN disease (ET or PV), before the bone marrow becomes fibrotic. Besides, a relatively small number of responders may still be beneficial, when taking into account the relatively low toxicity of these treatments.

Conflict of interests

None.

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