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Case Report

Resolution of Angina Pectoris in Five Patients with Myeloproliferative Neoplasms Treated with Pegylated Interferon Resistant Anginal: MPN Patient Treated with PEG-IFN

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ABSTRACT

The Philadelphia-negative chronic Myeloproliferative Neoplasms (MPNs) are characterised by the prevalence of somatic mutation *JAK2V617F* and associated with a high Cardiovascular Disease (CVD) burden, including ischemic heart disease with angina pectoris and heart failure, peripheral arterial insufficiency and risk the increase of such vascular malformations as aneurisms. Firing of the mutant Janus Kinase/Signal Transducers And Activators Of Transcription (JAK-STAT) signal transduction pathway results in blood cell count increase and induces the differentiation and maturation process of platelets and neutrophils. All these concomitant processes enhance the establishment of chronic inflammatory and thrombogenic state with a 12-times higher risk of coronary disease as a consequence. Long-term administration of Interferon-Alpha2 (rIFN) is proven to reduce the *JAK2V617F* allelic burden and minimise the risk of thrombotic events. Our first case report has already been published about a *CHIP-JAK2V617F* patient, who had gained remarkable relief of his treatment resistant angina pectoris due to a low dose of rIFN. Our present report describes five angina pectoris patient cases who had been diagnosed with MPN as well and showed significant improvement of their cardiological disease, refractor to previous therapy, instantly after the start of treatment with rIFN. The pathophysiological mechanisms behind such a remarkable rIFN-induced anti-angina pectoris effect is discussed hereafter. Our previous report and this series of patients call for the launch of explorative investigation of the rIFN effect on patients with CVD and MPN comorbidities or with *CHIP-JAK2V617F* disease predisposition.

Key points: 1. Complete resolution of angina pectoris is reported in five *JAK2V617F*-positive MPN-patients with severe ischemic heart disease during treatment with rIFN. 2. Targeting the *JAK2V617F* mutation by rIFN may favourably impact the CVD disease burden in MPNs to be pursued in future trials.

Keywords: *JAK2V617F* mutation; Myeloproliferative neoplasms (MPNs); Angina pectoris; Recombinant interferon-alpha2 and Recombinant interferon (rIFN)

Abbreviations: ET: Essential Thrombocythemia; PV: Polycythemia Vera; *AP: Angina Pectoris Treatment: generally after urgent coronarography + PCI+DES, double TAG (ASA+clopidogrel), rosuvastatin, beta blocker; PCI: Percutan Coronary Intervention; DES: Drug Eluting Stent; MI: Myocardial Infarction; LAD: Left Arteriol Descendent; RCA: Right Coronary Artery

INTRODUCTION

In recent years several studies have convincingly demonstrated acquired age-dependent somatic mutations in myeloid blood cells (*TET2*, *DNMT3A* and *JAK2V617F*) to be associated with increased cardiovascular diseases [1-14]. The disease complex of the Philadelphia-chromosome negative Myeloproliferative Neoplasms (MPNs) consists of Essential Thrombocythemia (ET), Polycythemia Vera (PV) and Primary Myelofibrosis (PMF). Onset of any of them is induced by somatic driver mutations, of which the *JAK2V617F* mutation is the predominant affecting

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about 98% of PV patients and 50%-60% of patients with ET or PMF. The *JAK2V617F* mutation generates Reactive Oxygen Species (ROS) which trigger the establishment of a chronic inflammatory state. It is claimed to contribute to the states of atherosclerosis and atherothrombosis with a 12-fold risk increase of coronary disease [15-18]. Other cofactor is the *JAK2V617F*-induced expression increase of Peptidyl Arginine Deiminase Type 4 (PAD4), which is an effector molecule in formation of *JAK2V617F*-driven Neutrophil Extracellular Traps (NETs), and also involved in thrombosis [19].

Elevated blood cell counts and constitutive *in vivo* activation of neutrophils and platelets with an inherent propensity to induce circulating micro aggregates of blood cells and thereby a decrease in blood flow in the microcirculation are other thrombogenic factors contributing significantly to morbidity and mortality in MPNs [15,16]. It can be viewed as a significant benefit of the pegylated Interferon Alpha2 (rIFN) treatment of MPNs patients with increased risk of thrombosis, that the compound reduces the *JAK2V617F* burden even lowers it to the level of 0.001% in a smaller proportion of patient cohort [20-34]. This way, rIFN normalizes the functionality of bone marrow and establishes the Minimal Residual Disease (MRD) status [35,36]. The first pegylated interferon-alpfa2b (ropeginterferon, or Besremi) has been registered and launched for treatment of PV upon the proof of several safety and efficacy studies [37-41]. Establishment of state of Clonal Hematopoiesis of Indeterminate Potential (CHIP) precedes the onset of MPNs for decades [1-14]. Most recent findings have highlighted the more remarkable prevalence of *JAK2V617F* mutation in the symptom free population than it was suspected with 5% in people older than 60 years. It leads to conclude that the MPN disease complex as a chronic blood cancer is massively underdiagnosed [42]. It has also been recorded that the CHIP-status of the *JAK2V617F* mutation is featured with increased incidence of thrombosis [19,42,43]. Modelling by mathematical algorithms has highlighted that, the earlier rIFN treatment of MPN the better, as its intense effect decreases *JAK2V617F* burden more rapidly [44].

CASE PRESENTATION

We have recently reported a case study of a *CHIP-JAK2V617F* positive patient who suffered severe angina pectoris and it rapidly resolved due to the rIFN treatment [45]. Herein, we report five patients with MPNs and severe ischemic heart disease with treatment-refractory angina pectoris. All patients experienced rapid improvement in angina pectoris during treatment with rIFN.

Clinical and biochemical data

All patients had MPNs for several years and all had been thoroughly investigated and treated for ischemic heart disease. Detailed information on individual patients is given in Table 1.

Table 1: Clinical characteristics of five patients with MPNs, in whom after PCI+DES implant +AP treatment resistant angina pectoris occurred and the severe angina pectoris resolved promptly during treatment with PEG-IFN.

Patient No.	Diagnosis	*JAK2V617F/VAF* (%)	Age (years) / Gender	Dg of Disease	Start of PEG-IFN	Comments
1	PV	pos/17	35/male	Oct/2021	May/2022 symptom free	Successful resuscitation, because ventricular fibrillation (during playing football), LAD PCI +DES, anginal complaints
2	PV	pos/5	61/male	Aug/2020	Jun/2021 symptom free	MI in 2012, after 6 months of HU cytoreduction, change to ruxolitinib, continuous anginal complaints change to Ropeg IFN
3	PV	pos/84	64/male	May/2019	Mar/2023 symptom free	MI in 2019, PCI+DES, stroke on HU cytoreduction, OCT/2022 ruxolitinib, anginal complaints change to Ropeg IFN
4	masked PV	pos/49	64/female	Mar/2019	Feb/2023 symptom free	MI in 2019, RCA PCI+DES, HU+ASA, anginal complaints Ropeg IFN
5	ET	pos/28	42/male	Dec/2018	Dec/2019 symptom free	MI in 2018, anginal complaints, Peginterferon alfa2a

Interpretation

These Case Reports convincingly demonstrate a strong correlation between resolution of angina complaints and initiation of treatment with rIFN.

Urgent questions to be discussed

- What are the mechanisms of action of rIFN in the context of resolution of angina pectoris?
- Should our report on a remarkable impact of rIFN in terms of resolution of angina pectoris be translated into an exploratory study on the safety and efficacy of rIFN in treatment-refractory angina pectoris patients, who harbour the *JAK2V617F* mutation?

RESULTS AND DISCUSSION

Long term treatment with rIFN has already been proved by several studies to normalize the cell counts in MPN-patients and to decrease the *JAK2V617F* burden, accordingly impacting several thrombosis promoting factors in MPNs [25-41]. We have recently reported a prompt resolution of severe angina pectoris in a *CHIP-JAK2V617F* patient [45]. We speculated, whether the amazing effect might be associated with an IFN-induced decrease in several factors, which are considered influential for triggering angina pectoris, including elevated blood cell counts, *in vivo* leukocyte, platelet and endothelial activation, and oxidative stress [45]. By inducing constitutive JAK-STAT signalling the JAK2V617 mutation gives rise to all the above inflammation-mediating and thrombosis-promoting factors [15-16]. Therefore, we suggested that the *JAK2V617F* mutation might be a novel therapeutic target to alleviate angina pectoris in otherwise treatment-resistant patients [45]. This report adds further evidence that rIFN might be a highly potent agent in the treatment of severe angina pectoris. Thus, all our patients responded promptly to treatment with rIFN. Recent knowledge on chronic inflammation considers it to be an important pathogenetic mechanism in development of MPN-diseases and in their progression [20-24]. The upregulated thrombo-inflammatory genes in MPN-patients are supposed to contribute to the increase of risk of thrombotic events [15,46]. In addition, whole blood gene expression studies have been performed to show that the rIFN treatment normoregulates or even more, downregulates the previously upregulated thrombo-inflammatory genes, including the PAD4 [45]. The latter one involved in escalation of NETosis and thereby the onset of thrombotic events [19]. Furthermore, the compound of rIFN switches down the upregulated oxidative stress genes and reactivates the downregulated antioxidative defence genes [47,48]. We believe that the present report calls for studies to investigate the role of rIFN in the CVD burden in *JAK2V617F* positive MPN-patients and in *CHIP-JAK2V617F*-positive individuals, as well. Such studies should include both explorative investigations and well-designed clinical trials. Previous ones should include serial transcriptomic, proteomic and thrombophilia studies as well. They may discover the mechanisms behind the beneficial effects of rIFN in symptom burden and functional improvement in CVD. Furthermore, they may also inlight the regression and calcifications of coronary and aortic valves, which are prominent in patients with MPNs and likely comes with the *JAK2V617F* mutation in association of ischemic heart diseases [49,50]. This fact has been shown in large Danish Register study [50].

CONCLUSION

In conclusion, herein, we have added further evidence that rIFN treatment might have a role in the treatment of "refractory angina pectoris". The beneficial effects might be related to the anti-inflammatory and anti-thrombotic potentials of rIFN, including reduction of oxidative stress and ROS together with downregulation of thrombo-inflammatory genes. Our report puts in perspective the need of clinical studies of the impact of rIFN upon the CVD burden both in the CHIP-stage and in patients with MPNs.

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