Complete molecular remission in a polycythaemia vera patient 12 years after discontinuation of interferon-alpha

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Abstract: IFN-alpha can produce regression of splenomegaly and control of peripheral blood counts in patients with myeloproliferative disorders for prolonged periods even after discontinuation. We describe a patient with polycythemia vera who is in complete haematological and molecular remission despite stopping IFN-alpha twelve years ago.

Response to Reviewers: We have revised our manuscript to address the various points made by the referee - the changes appear in red. Specifically:

1. I would like to know the clinico-hematological and histological status of the patient when the complete molecular remission has been observed (October 2009);
2. For a better comparison with the retrospective evaluations, a confirmation of the complete molecular remission also in bone marrow is worthwhile;

Reply to first 2 points: 'As the patient remained completely asymptomatic with normal physical examination and normal complete blood count and as the JAK2 V617F allele burden is reportedly equivalent in peripheral blood and bone marrow [7], bone marrow examination was not repeated.'

3. Is it possible to obtain a quantitative estimation of the JAK2 mutated allele burden ?

Response: 'Although quantitation of mutated JAK2 alleles was not performed, demonstration of a reduction of the mutated clone in the 1997 bone marrow sample compared to that at diagnosis might have provided some support for our hypothesis.'

4. The authors suggested that IFN caused a sufficient suppression of the mutated clone to allow a subsequent full expansion of normal haematopoietic cells. This intriguing hypothesis should be more extensively explained and referenced.

Reply:

'Nevertheless, development of polyclonal haematopoiesis after IFN-alpha treatment has been described in PV patients despite persistent, although reduced, expression of the JAK2 V617F mutation [10]. In cultured CD34+ cells, isolated from patients with newly diagnosed chronic myeloid leukemia (CML), treatment with IFN-alpha causes greater toxicity to primitive progenitors responsible for the maintenance of long-term cultures compared to more differentiated CML progenitors, whilst the majority of primitive Philadelphia chromosome negative progenitors survived [11]. These findings support the possibility that IFN-alpha might sufficiently suppress the malignant clone in myeloproliferative disorders to allow re-establishment of normal hematopoiesis. In addition, an

increase in absolute numbers of CD19+ and CD56+ lymphocytes in CML patients achieving a cytogenetic complete remission with IFN-alpha compared to patients with lesser responses has been noted [12]. Thus, an alternative or complementary explanation for the delayed achievement of complete molecular remission in our patient is that, following discontinuation of IFN-alpha, eradication of the residual JAK2 V617F mutated clone was achieved by persistent immune modulatory properties of IFN-alpha.'

Please see revised manuscript for references.

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LETTER TO THE EDITOR

Complete molecular remission in a polycythaemia vera patient twelve years after discontinuation of interferon-alpha

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Dear Editor,

We read with interest the recent report of a sustained molecular remission of 12 months follow-up after discontinuation of interferon-alpha-2b (IFN-alpha) in a patient with polycythemia vera (PV) [1]. IFN-alpha can produce regression of splenomegaly and control of peripheral blood counts in patients with myeloproliferative disorders for prolonged periods even after discontinuation [2]. Recently, the *JAK2* V617F mutation has become a reliable disease marker in most cases of PV with detection and quantitation of mutated *JAK2* alleles potentially useful in monitoring the effects of treatments such as IFN-alpha [3,4] and a plethora of novel *JAK2* inhibitors [5]. We describe a patient with PV who is in complete haematological and molecular remission despite stopping IFN-alpha twelve years ago.

A 19-year-old male presented in November 1990 with haemoglobin (Hb) 6.4 g/dl, red cell count $3.94 \times 10^{12}/l$, MCV 52 fl, platelet count $491 \times 10^9/l$ and with a normal white cell count and differential. He had a 4 cm palpable spleen. Trephine biopsy was hypercellular with increased erythropoiesis, myelopoiesis and megakaryopoiesis but no increase in reticulin staining. Bone marrow cytogenetics were normal. He was treated with oral iron, which was discontinued in April 1991 when Hb increased to 18.2 g/dl. An increase in red cell mass of 50.2 ml/Kg confirmed a diagnosis of PV and was controlled by intermittent venesection until February 1993, when he started treatment with IFN-alpha-2b 3 million units sc three times weekly. Complete blood counts have subsequently remained in normal range, whilst the patient's spleen has remained impalpable since October 1994. Repeat BMA and trephine biopsy in September 1997, whilst showing erythroid hyperplasia and increased numbers of megakaryocytes, were much less hypercellular than at diagnosis. In November 1997, IFN-alpha was discontinued because of fatigue. In October 2009, the *JAK2* V617F mutation was undetected in DNA extracted from whole peripheral blood using a previously described allele-specific PCR technique [6]. This methodology is capable of detecting a heterozygous mutation in 2% of total cells from either peripheral blood or bone marrow. As the patient remained completely asymptomatic with normal physical examination and normal complete blood count and as the *JAK2* V617F allele burden is reportedly equivalent in peripheral blood and bone marrow [7], bone marrow examination was not repeated. DNA extracted from archival bone marrow aspirate slides from November 1990 and September 1997 were both subsequently found to harbour the *JAK2* V617F mutation.

1 In two recently reported phase two studies of peg-IFN-alpha-2a in PV patients, complete
2 molecular remissions were obtained in 7/26 (27%) of responding patients and in 14% of 35
3 evaluable patients [3,4]. In this case, peripheral blood taken twelve years after stopping a
4 four year course of IFN-alpha displayed a complete molecular remission according to
5 consensus guidelines [8]. In our patient, it is noteworthy that a bone marrow sample in 1997
6 just prior to IFN-alpha discontinuation was still positive for the JAK2 V617F mutation, yet a
7 peripheral blood sample 12 years later was negative for this mutation. Although remission
8 unrelated to treatment remains a possibility [9], we hypothesise that IFN-alpha caused a
9 sufficient suppression of the JAK2 V617F bearing clone to subsequently allow full expansion
10 of normal haematopoietic elements. Although quantitation of mutated JAK2 alleles was not
11 performed, demonstration of a reduction of the mutated clone in the 1997 bone marrow
12 sample compared to that at diagnosis might have provided some support for our hypothesis.
13 Nevertheless, development of polyclonal haematopoiesis after IFN-alpha treatment has
14 been described in PV patients despite persistent, although reduced, expression of the JAK2
15 V617F mutation [10]. In cultured CD34+ cells, isolated from patients with newly diagnosed
16 chronic myeloid leukemia (CML), treatment with IFN-alpha causes greater toxicity to
17 primitive progenitors responsible for the maintenance of long-term cultures compared to
18 more differentiated CML progenitors, whilst the majority of primitive Philadelphia
19 chromosome negative progenitors survived [11]. These findings support the possibility
20 that IFN-alpha might sufficiently suppress the malignant clone in myeloproliferative
21 disorders to allow re-establishment of normal hematopoiesis. In addition, an increase in
22 absolute numbers of CD19+ and CD56+ lymphocytes in CML patients achieving a
23 cytogenetic complete remission with IFN-alpha compared to patients with lesser
24 responses has been noted [12]. Thus, an alternative or complementary explanation for
25 the delayed achievement of complete molecular remission in our patient is that, following
26 discontinuation of IFN-alpha, eradication of the residual JAK2 V617F mutated clone was
27 achieved by persistent immune modulatory properties of IFN-alpha. We are unaware of
28 any similar, documented case of PV in long term complete molecular remission so many
29 years after stopping IFN-alpha treatment with this case adding further evidence of the utility
30 of IFN-alpha in PV patients, including those diagnosed at a relatively young age.

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