Decrease in *JAK2*^{V617F} allele burden is not a prerequisite to clinical response in patients with polycythemia vera

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ABSTRACT

Background

Although reduction in the *JAK2*^{V617F} allele burden (%*V617F*) has been suggested as a criterion for defining disease response to cytoreductive therapy in polycythemia vera, its value as a response monitor is unclear. The purpose of this study is to determine whether a reduction in %*V617F* in polycythemia vera is a prerequisite to achieving hematologic remission in response to cytoreductive therapy.

Design and Methods

We compared the clinical and hematologic responses to change in %*V617F* (molecular response) in 73 patients with polycythemia vera treated with either interferon (rIFNα-2b: 28, Peg-rIFNα-2a: 18) or non-interferon drugs (n=27), which included hydroxyurea (n=8), imatinib (n=12), dasatinib (n=5), busulfan (n=1), and radioactive phosphorus (n=1). Hematologic response evaluation employed Polycythemia Vera Study Group criteria, and molecular response evaluation, European Leukemia Net criteria.

Results

Of the 46 treated with interferon, 41 (89.1%) had a hematologic response, whereas only 7 (15.2%) had a partial molecular response. Of the 27 who received non-interferon treatments, 16 (59.3%) had a hematologic response, but only 2 (7.4%) had a molecular response. Median duration of follow up was 2.8 years. Statistical agreement between hematologic response and molecular response was poor in all treatment groups.

Conclusions

Generally, hematologic response was not accompanied by molecular response. Therefore, a quantitative change in %*V617F* is not required for clinical response in patients with polycythemia vera.

Key words: JAK2V617F, molecular response, polycythemia vera, reduced allele burden.

Citation: Kuriakose E, Vandris K, Wang YL, Chow W, Jones AV, Christos P, Cross NCP, and Silver RT. Decrease in JAK2V617F allele burden is not a prerequisite to clinical response in patients with polycythemia vera. Haematologica 2012;97(4):538-542. doi:10.3324/haematol.2011.053348

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Funding: this work was supported by the William and Judy Higgins Trust and the Johns Family Fund of the Cancer Research and Treatment Fund Inc., New York, NY, USA. PC was partially supported by a grant from the Clinical Translational Science Center (CTSC) (UL1-RR024996).
Presented in part at the 51st American Society of Hematology Annual Meeting and Exposition, New Orleans, LA, USA, December 5-8, 2009. (ASH Annual Meeting Abstracts, Nov 2009; 114:1908).

Manuscript received on August 9, 2011. Revised version arrived on October 26, 2011. Manuscript accepted on November 3, 2011.

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Introduction

The finding of the *JAK2V617F* mutation and other *JAK2* mutations (exon 12 in *V617F*-negative PV) in essentially all patients with PV1,[1-4] is established in the pathogenesis and diagnosis of PV.[1,3,5] Reducing the *JAK2*^{V617F} allele burden is one of the criteria used in defining disease response to treatment in patients with PV by the European LeukemiaNet (ELN) Working Group,[6] but the pathogenetic and clinical significance of a decrease in the *JAK2*^{V617F} allele burden remains uncertain.

In a previous study of 37 evaluable patients treated with pegylated recombinant interferon alpha-2a (Peg-rIFNα-2a), all 37 (100%) achieved hematologic response,[7] but sequential samples for *JAK2*^{V617F} monitoring were available in only 29.[7] Twenty-one of 29 (72.4%) had a decrease of at least 50% in the *JAK2*^{V617F} allele burden after 24 months of treatment, implying that hematologic and molecular response in PV are strongly correlated.[7] However, in another study of 40 patients with PV treated with Peg-rIFNα-2a, 80% had a hematologic response, but only 54.3% had a molecular response after a median of 21 months.[8] In comparison, we reported that in 25 patients treated with recombinant interferon-alpha-2b (rIFNα-2b), only 4 (16%) had a partial molecular response despite excellent clinical and hematologic responses after a median duration of follow up of one year (range 0.1-3.6 years).[9]

The effect of various non-interferon treatments on the *JAK2*^{V617F} allele burden in PV has also been ambiguous, with some showing significant molecular responses[10-14] and others not.[15-17] The well-characterized hematologic responses in patients with PV treated with imatinib showed no significant molecular responses.[18-20]

We report our experience with 73 patients with PV treated with rIFNα-2b, Peg-rIFNα-2a, and non-interferon protocol treatments. We assessed the importance of the association between hematologic (clinical) response and molecular response, as defined by the criteria of the Polycythemia Vera Study Group (PVSG), and the European LeukemiaNet Working Group (ELN), respectively.[6]

Design and Methods

Patient selection and evaluation

The clinical diagnosis of PV in 73 sequential patients was based upon demonstration of an increased Cr^{51} red blood cell mass and simultaneously determined I^{125} plasma volume and other PVSG diagnostic criteria,[21] and on demonstration of a *JAK2* molecular abnormality. Internal Review Board approval and written informed consent were obtained. White blood cell (wbc) and differential count, hematocrit value (hct), platelet count (plt), and spleen size were measured at the time of *JAK2* analysis. Spleen size, measured in centimeters (cm) below the mid-point of the left costal margin in the mid-clavicular line, was categorized as not (<1 cm), slightly (1-3 cm), moderately (4-9 cm), or grossly (>9 cm) enlarged.

Clinical and hematologic response criteria

Clinical and hematologic responses were graded according to modified criteria of the PVSG.[22] Complete hematologic response (CHR) was defined as: freedom from phlebotomy (phl), hct 45% or under for men and 42% or under for women, plt 600×10^9/L or under, and absent splenomegaly. Partial hematologic response (PHR) was defined as 50% or over reduction in phl requirement, plt 600×10^9/L or under, and any degree of persistent splenomegaly. No hematologic response (NHR) was defined as failure to meet the criteria of CHR or PHR.

JAK2^{V617F} assessment and molecular response criteria

Serial quantified measurements of the *JAK2*^{V617F} allele burden were performed by a standard method at 6-month intervals over a median of 1.6 years (range 0.2-7.3 years). DNA used for genotyping was purified from total white blood cells collected from peripheral blood. *JAK2*^{V617F} levels were determined by pyrosequencing, a method that quantifies *JAK2*^{V617F} when the mutant allele is over 5%.[3] Molecular response was graded according to ELN criteria as previously described.[6]

Treatment groups

Interferon alpha (rIFNα)

Forty-six patients were treated with interferon. Of these, 28 patients were treated with rIFNα-2b in doses ranging from 0.5 million units (MU) to 3.0 MU three times weekly, depending upon tolerance and clinical response. Eighteen patients were treated with Peg-rIFNα-2a at doses ranging from 15 to 225 μg subcutaneously per week, with a median dose of 90 μg per week. Median treatment durations for rIFNα-2b and Peg-rIFNα-2a were 6.8 years (range 0.7-16.9 years) and 1.6 years (range 0.6-2.3 years), respectively.

Non-interferon treatments

Twenty-seven patients were treated with drugs other than interferon. The median treatment duration was 3.0 years (range 0.3-8.0 years). Drugs and doses were: imatinib mesylate initially 400 mg daily increased to 600 mg or 800 mg daily, if necessary, for lack of response; dasatinib 100 mg daily with increase to 120 mg daily for lack of response; hydroxyurea 500 mg to 2000 mg daily; P-32 4.3 mCi intravenously; busulfan 4 mg daily. In addition, phlebotomy was performed as needed to maintain hct 45% or under for men and 42% or under for women.

Statistical analysis

The kappa statistic was used to quantify the degree of agreement between hematologic and molecular response. Kappa values more than 0.75 indicate excellent agreement, between 0.4 and 0.75 good agreement, and less than 0.4 indicate marginal or poor agreement. A value less than or equal to 0.0 indicates no agreement. Wilcoxon's signed rank test was used to compare serial (initial *vs.* final) *JAK2*^{V617F} allele burden determinations for all patients experiencing either a complete or partial hematolgic response. Comparisons of initial and final *JAK2*^{V617F} allele burden determinations were also stratified by type of treatment. All *P* values were two-sided with statistical significance evaluated at the 0.05 alpha level. All analyses were performed in SPSS Version 19.0 (SPSS Inc., Chicago, IL, USA).

Results

Patients' characteristics

The median age at diagnosis of our 73 patients was 53 years; 38 patients (52.1%) were men. Sixty-six patients were phlebotomy-dependent with a median requirement of 4 phlebotomies per year (range 1-12). Median wbc, hct, and plt were 12.1×10^9/L (range 3.9×10^9/L - 35.7×10^9/L), 43.1% (range 34.8-52.8%), and 444×10^9/L (range 74×10^9/L - 1696×10^9/L), respectively. Median duration of follow up was 2.8 years (range 0.3-16.9 years).

Hematologic and molecular response

Interferon treatment group

Of all 46 patients treated with interferon, 41 (89.1%) had a hematologic response [CHR 12 (26.1%); PHR 29 (63%)], and 7 (15.2%) had a PMolR (CHR 4; PHR 2; NHR 1). Of the 18 patients treated with Peg-rIFNα-2a, 16 (88.9%) had a hematologic response [CHR 3 (16.7%); PHR 13 (72.2%)], but only one (5.6%) had a molecular response (PHR+PMolR). Of the 28 patients treated with rIFNα-2b, 25 (89.3%) had a hematologic response [CHR 9 (32.1%); PHR 16 (57.2%)], but only 6 (21.4%) had a partial molecular response (Figure 1). To summarize, of the 46 patients treated with interferon, 7 (15.2%) had a partial molecular response. Notably, one patient treated with rIFNα-2b had a PMolR without a hematologic response (NHR). There were no CMolRs in interferon-treated patients.

There was no significant change in the median *JAK2*^{V617F} allele burden in any of the patients treated with interferon over a median follow-up period of 1.6 years (range 0.2-6.7 years). Among the patients who achieved CHR or PHR, the median *JAK2*^{V617F} allele burden at the beginning and end of follow up was 72.1 and 68.6% in those treated with Peg-rIFNα-2a (P=0.18) (Figure 2A), and 42.3 and 52.5% in those treated with rIFNα-2b (P=0.26), respectively (Figure 2B).

Non-interferon treatment group

Of the 27 patients who received non-interferon treatments, 16 (59.3%) had a hematologic response [9 CHR (33.3%) and 7 PHR (25.9%)]. Two patients (7.4%) had a molecular response: one CMolR (busulfan) and one PMolR (imatinib) (Figure 1). Hematologic and molecular responses for the non-interferon treatments were: hydroxyurea 8 patients (n=5 HR/NMolR, n=3 NHR/NMolR), imatinib 12 patients n=1 PHR/PMolR, n=8 HR/NMolR, n=3 NHR/NMolR), dasatinib 5 patients (n=1 PHR/NMolR, n=4 NHR/NMolR), busulfan one patient (n=1 CHR/CMolR) and P-32 one patient (n=1 NHR/NMolR). The median *JAK2*^{V617F} allele burden for all 27 patients at the beginning and end of a median follow-up period of 1.5 years (range 0.2-7.3 years) was 46.1 and 42.6%, respectively (P=0.06). Of those who had a hematologic response (CHR or PHR), the median *JAK2*^{V617F} allele burden was 41.4 and 31.5%, respectively (P=0.33) over the course of the follow-up period (Figure 2C).

Hematologic and molecular response correlation

The statistical agreement between hematologic response (CHR + PHR) and molecular response (CMolR + PMolR) in all treatment groups was poor (all treatments combined, kappa coefficient (k)=0.04, P=0.40; interferon treatment group: k=-0.01, P=0.75; non-interferon treatment group: k=0.10, P=0.22).

Discussion

It is implicit in the reports of reduction in the *JAK2*^{V617F} allele burden with treatment that it correlates with clinical response.[7,8,10-14] Our data indicate, however, that decrease in *JAK2*^{V617F} allele burden does not correlate with clinical and hematologic response, despite different treatments.

We previously reported the lack of substantial change in *JAK2*^{V617F} allele burden in patients treated with rIFNα-2b.[9,20] Sequential decrease in *JAK2*^{V617F} allele burden has been reported with Peg-rIFNα-2a,[7,8,23-25] but our patients treated with Peg-rIFNα-2a had no significant change. In studies showing this molecular response,[7,8,23-25] at least a PMolR was seen after 6-12 months of treatment. Since our patients receiving Peg-rIFNα-2a were treated for a median of 19.2 months, the lack of molecular response cannot be attributed to inadequate duration of treatment *per se*.

In the studies indicating molecular responses in more than 50% of patients treated with Peg-rIFNα-2a,[8,25] the starting and maintenance doses were, on average, 1.5 to 2 times those used in our patients.[7,8] The discontinuation rates due to toxicity in these studies were 24.3% (Kiladjian *et al.*) and 10% (Quintas-Cardama *et al.*).[7,8] The median dose of Peg-rIFNα-2a in our patients was 90.0 μg per week, with a 6% discontinuation rate due to toxicity, over a period of 19.2 months.[7,8] This dose may account for the decreased molecular responses we observed. Despite this, nearly 90% (88.9%) of our patients had a hematologic response with excellent tolerance. This suggests that higher doses of Peg-rIFNα-2a are required for molecular response but at the cost of increased toxicity, whereas durable clinical and hematologic responses can be obtained with lower, more tolerable doses. The variability of response to interferon may reflect individual differences in drug metabolism and/or disease heterogeneity, perhaps related to genetic and molecular factors requiring further characterization.[26] Long-term prospective studies are needed to determine if therapeutically targeting to complete molecular response is clinically meaningful in PV.

Non-interferon treatments

The majority of patients in the non-interferon group were treated with hydroxyurea (HU) or imatinib. As reported by others,[15-17] approximately two-thirds (62.5%) of our patients treated with hydroxyurea had a hematologic response but no molecular response. In those studies using HU in which the *JAK2*^{V617F} allele burden declined, most patients were

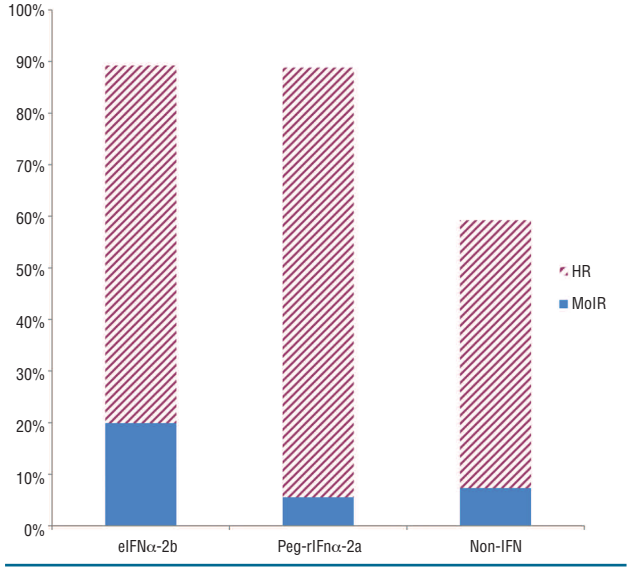

Figure 1. Proportion of molecular response (CmolR + PMolR) in patients with hematologic response (CHR + PHR). MolR: molecular response; CmolR: complete molecular response; PmolR: partial molecular response; HR: hematologic response; CHR: complete hematologic response; PHR: partial hematologic response; rIFNα-2b: recombinant interferon alpha-2b therapy; Peg-rIFNα-2b: pegylated recombinant interferon alpha-2a therapy; Non-IFN: non-interferon therapy.

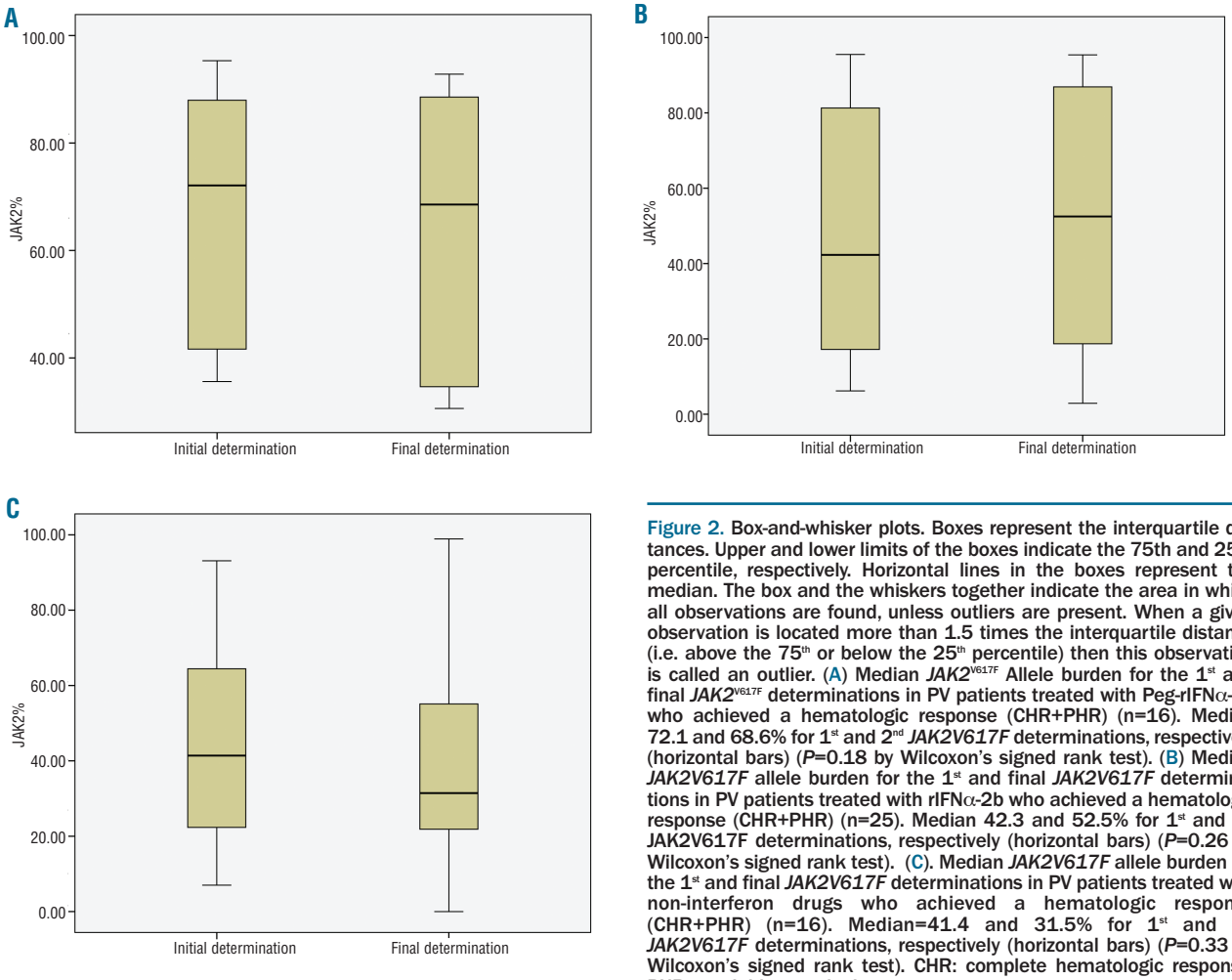

Figure 2. Box-and-whisker plots. Boxes represent the interquartile distances. Upper and lower limits of the boxes indicate the 75th and 25th percentile, respectively. Horizontal lines in the boxes represent the median. The box and the whiskers together indicate the area in which all observations are found, unless outliers are present. When a given observation is located more than 1.5 times the interquartile distance (i.e. above the 75th or below the 25th percentile) then this observation is called an outlier. (A) Median *JAK2*^{V617F} Allele burden for the 1st and final *JAK2*^{V617F} determinations in PV patients treated with Peg-rIFNα-2a who achieved a hematologic response (CHR+PHR) (n=16). Median 72.1 and 68.6% for 1st and 2nd *JAK2V617F* determinations, respectively (horizontal bars) (*P*=0.18 by Wilcoxon's signed rank test). (B) Median *JAK2V617F* allele burden for the 1st and final *JAK2V617F* determinations in PV patients treated with rIFNα-2b who achieved a hematologic response (CHR+PHR) (n=25). Median 42.3 and 52.5% for 1st and 2nd JAK2V617F determinations, respectively (horizontal bars) (*P*=0.26 by Wilcoxon's signed rank test). (C). Median *JAK2V617F* allele burden for the 1st and final *JAK2V617F* determinations in PV patients treated with non-interferon drugs who achieved a hematologic response (CHR+PHR) (n=16). Median=41.4 and 31.5% for 1st and 2nd *JAK2V617F* determinations, respectively (horizontal bars) (*P*=0.33 by Wilcoxon's signed rank test). CHR: complete hematologic response; PHR: partial hematologic response.

newly diagnosed and treatment naïve, and had varying molecular responses.[12-14] In these studies, median time to at least PMoIR was 12-14 months. Therefore, the lack of a similar response in our patients, treated for a median of 5.6 years, cannot be attributed to inadequate duration of treatment. The median dose of HU used in our patients was similar to those studies reporting substantial molecular response.[12-14] Like interferon, the variability of response to HU may reflect individual differences in drug metabolism and/or disease heterogeneity related to other genetic and molecular factors, as previously mentioned.[26]

Although we and others have reported significant hematologic and clinical responses in imatinib-treated patients,[18,19] none reported significant molecular responses, as confirmed in 75% of our imatinib-treated patients who had a hematologic response. This fact, combined with a moderate degree of toxicity to imatinib, will probably limit its use to selected patients with PV.[27]

Only one patient in our study had both a CHR and a CMoIR that occurred in a patient treated with busulfan. This probably reflects its potency as a non-specific cytotoxic agent[28,29] rather than as a modulator of mutant *JAK2*.

Of our 73 patients with a quantifiable *JAK2*^{V617F} allele burden, 66 received treatment prior to the initial *JAK2* determination for a median duration of 6.3 years. Therefore, it is conceivable that these patients had pre-existing molecular responses, especially in those with a first *JAK2*^{V617F} allele burden of less than 75% (the minimum required by the ELN criteria for at least a PMolR). However, two factors argue against this possibility. First, continued molecular response did not occur over the ensuing follow-up period, despite continued hematologic response and adequate treatment duration. Second, even if there was a molecular response to previous treatment, it would be unlikely that a plateau in response occurred at the study start point in multiple treatment groups.

We and others have shown that, in general, a high *JAK2*^{V617F} allele burden (>50%) is associated with a more severe disease phenotype.[23] It may, therefore, seem intuitive to use *JAK2*^{V617F} allele burden as a marker for evaluating treatment response. However, our finding that disease phenotype can improve without molecular response suggests that the association between high *JAK2* allele burden with worse clinical phenotype is coincidental, not causal.[9] Hence, additional genetic or epigenetic mechanisms modulated through *JAK2* and other signaling pathways may contribute to the phenotypic variations observed in PV.[26,30]

Conclusion

Although the presence of the *JAK2*^{V617F} allele plays a vital role in the diagnosis of PV, quantitative change in the *JAK2* allele burden may not be a unique pathogenic measure of

clinical and hematologic response to therapy with cytoreductive drugs, comparable, for example, to BCR-ABL in chronic myeloid leukemia. The prognostic value of attaining a molecular response in PV patients with hematologic remission remains unresolved. Prospective studies are needed to assess the significance of attaining a complete molecular response in those patients with clinical and hematologic remission, compared to those who do not.

Authorship and Disclosures

The information provided by the authors about contributions from persons listed as authors and in acknowledgments is available with the full text of this paper at www.haematologica.org.

Financial and other disclosures provided by the authors using the ICMJE (www.icmje.org) Uniform Format for Disclosure of Competing Interests are also available at www.haematologica.org.

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