To the editor:

**JAK2V617F complete molecular remission in polycythemia vera/essential thrombocythemia patients treated with ruxolitinib**

Polycythemia vera (PV) and essential thrombocythemia (ET) are characterized by JAK2V617F mutation in 95% and 60% of the patients, respectively. JAK2 inhibitor ruxolitinib has been approved for the treatment of myelofibrosis (MF) and more recently for hydroxyurea resistant/intolerant PV patients because of its superiority to standard therapy (and placebo in MF) in improving splenomegaly, ameliorating symptoms, and reducing phlebotomies (in PV). Among 13 patients showing a sustained reduction of JAK2V617F allele burden from baseline at 72 weeks was observed in MF patients in the COMFORT-II study. A progressive decrease of the JAK2V617F allele burden by a mean of 22% at 36 months was reported in 34 PV patients enrolled in a phase 2 trial (INCB18424-256, ClinicalTrials.gov #NCT00726232) that also included 22 ET patients, with 23.5% of the patients achieving a ≥50% reduction; however, no complete molecular remission (CMR) was attained at that time. Comparably, in the phase 3 RESPONSE study in PV, the mean decrease of JAK2V617F allele burden at week 32 (n = 92) and at week 112 (n = 22) was 12.2% and 34.7%, respectively.

Twenty-two JAK2V617F-mutated patients, 11 PV and 11 ET, were enrolled in our center in the INCB18424-256 study, and 19 have been followed for >5 years. We measured the JAK2V617F allele burden by reverse-transcriptase quantitative polymerase chain reaction (RT-qPCR) assays (sensitivities of 0.8% and 0.08%), and deep amplicon resequencing (Ion Torrent platform). Approval was obtained from the Azienda Ospedaliero-Università Careggi institutional review board for these studies. Informed consent was provided according to the Declaration of Helsinki.

Our data confirmed the overall modest JAK2V617F allele burden reduction seen in previous studies in patients receiving ruxolitinib but indicated that some (16% in this series) may attain a JAK2V617F CMR and in 9% of MF patients treated with imetelstat. Reported effects of hydroxyurea were variable, with some series reporting CMR in 12% to 26% of ET patients and in 8% to 17% of PV patients, whereas other studies showed only modest allele burden decrease in few patients.

![Figure 1](https://example.com/figure1.png)

**Figure 1. JAK2V617F allele burden decrease in patients achieving >25% reduction at 60 months and details of patients attaining complete molecular remission.** (A) The percentage decline over time (mean ± SD) of the JAK2V617F allele burden in the 13 patients who presented a >25% allele burden reduction at 60 months. JAK2V617F allele burden decreased by a mean of 7%, 11%, 19%, and 28% at 1, 2, 3, and 5 years, respectively. (B) The absolute level of JAK2V617F allele burden in the 3 patients (pt) who finally achieved a CMR at 5 years (confirmed 3 months later) is presented. Measurement of the JAK2V617F allele burden was performed in peripheral blood granulocytes by RT-qPCR. The attainment of CMR was further confirmed by both a high-sensitivity RT-qPCR assay (detection limit, 0.08%) and deep resequencing at 5 years and at 3-month time points. SD, standard deviation.
with prolonged treatment. The persistence of other mutations, such as TET2, may suggest biclonal disease or a single ancestral TET2-mutated founder clone later acquiring JAK2V617F; we could not distinguish between these 2 possibilities, lacking viable cells for clonal analysis.

The attainment of JAK2V617F CMR occurring notwithstanding the persistence of some PV- and ET-associated features might reclassify either additional clone(s) with unknown mutations insensitive to JAK2 inhibition or different kinetics of normalization of histologic and hematologic parameters. Larger studies are required to establish the frequency of CMR with JAK2 inhibitors and its relevance for the management of these chronic diseases.

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References


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