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Resolution of bone marrow fibrosis in a patient receiving JAK1/JAK2 inhibitor treatment with ruxolitinib

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Abstract

Ruxolitinib, a JAK1/JAK2 inhibitor, is currently the only pharmacological agent approved for the treatment of myelofibrosis. Approval was based on findings from two phase 3 trials comparing ruxolitinib with placebo (COMFORT-I) and with best available therapy (COMFORT-II) for the treatment of primary or secondary myelofibrosis. In those pivotal trials, ruxolitinib rapidly improved splenomegaly, disease-related symptoms, and quality of life and prolonged survival compared with both placebo and conventional treatments. However, for reasons that are currently unclear, there were only modest histomorphologic changes in the bone marrow, and only a subset of patients had significant reductions in JAK2 V617F clonal burden. Here, we describe a patient with post-polycythemia vera myelofibrosis who received ruxolitinib at our institution (Guy’s and St. Thomas’ NHS Foundation Trust, London, United Kingdom) as part of the COMFORT-II study (NCT00934544). While on treatment, the patient had dramatic improvements in splenomegaly and symptoms shortly after starting ruxolitinib. With longer treatment, the patient had marked reductions in JAK2 V617F allele burden, and fibrosis of the bone marrow resolved after approximately 3 years of ruxolitinib treatment. To our knowledge, this is the first detailed case report of resolution of fibrosis with a JAK1/JAK2 inhibitor.

Trial registration: ClinicalTrials.gov Identifier: NCT00934544

Introduction

Primary myelofibrosis (PMF) is a myeloproliferative neoplasm that is characterized clinically by bone marrow fibrosis, progressive anemia, and extramedullary hematopoiesis, which often manifests as splenomegaly.1,2 Myelofibrosis (MF) may also develop as a manifestation of disease progression in other myeloproliferative neoplasms, particularly polycythemia vera (PV) and essential thrombocythemia (ET). At the stage of MF in all of these conditions, symptoms arise largely from fibrotic bone marrow replacement. Primary symptoms include those resulting from anemia or splenomegaly (eg, early satiety, abdominal pain) and constitutional symptoms (ie, fever, weight loss, night sweats).3,4 Alleviation of these symptoms is a near-term goal of treatment, mainly because conventional therapies have been unable to meaningfully affect the biology of the disease.2

Allogeneic hematopoietic stem cell transplantation (AHSCT) is currently the only treatment option that has curative potential in MF.5 However, AHSCT is associated with significant morbidities, and most patients are not suitable candidates. Additionally, with the exception of AHSCT, no therapy has consistently been associated with stabilization or resolution of fibrosis in patients with MF. Findings that reflect resolution of bone marrow fibrosis with Janus kinase (JAK) inhibitor treatment have not been reported. This report describes a patient with post-PV MF who had a marked reduction in bone marrow fibrosis during treatment with the JAK1/JAK2 inhibitor ruxolitinib. To our knowledge, this is the first detailed report of such a case.

Methods

The patient was enrolled in the COMFORT-II trial and was randomized to the ruxolitinib arm.6 COMFORT-II is a randomized, open-label, multicenter study evaluating the safety and efficacy of ruxolitinib 15 or 20 mg twice daily (bid) compared with best available therapy for the treatment of PMF, post-PV MF, and post-ET MF. The primary endpoint was the proportion of patients who achieved a ≥ 35% reduction from baseline in spleen volume (ie, a spleen response) at week 48, as measured by magnetic
resonance imaging (MRI), and the key secondary endpoint was a spleen response at week 24. Secondary endpoints included overall survival, histopathologic characteristics of bone marrow, and analyses of symptoms and quality of life; dynamics of JAK2 V617F clonal burden was an exploratory endpoint of the trial. The study design and patient criteria were fully described previously. Of note, the starting dose was determined by the patient’s platelet count at baseline (15 mg bid for patients with a platelet count from 100 to $200 \times 10^9/L$ and 20 mg bid for patients with a platelet count $> 200 \times 10^9/L$), and the dose was titrated for each patient throughout the trial to optimize safety and efficacy. Dose reductions were required for thrombocytopenia and followed a strict protocol-defined dosing regimen. The last data cutoff for the COMFORT-II study was 1 December 2012; here, we report the latest on-study results for this patient as well as additional findings from our institution.

The study protocol was approved by the institutional review board prior to patient enrollment and the study was conducted in accordance with the principles set forth by the Declaration of Helsinki.

Results—Case Report

A 74-year-old male patient presented to our clinic with constitutional symptoms (night sweats and fever), pruritus, and marked splenomegaly of 26 cm below the left costal margin (spleen volume: $3390 \text{ cm}^3$). He had received a diagnosis of PV 10 years previously, in 1999, and had been receiving treatment with hydroxycarbamide (HC) since the initial diagnosis. Comorbidities included hypertension and monoclonal gammopathy, both of which were found at the time of PV diagnosis.

A diagnosis of post-PV MF with a risk category of International Prognostic Scoring System (IPSS) criteria intermediate-2 (age > 65 years and presence of constitutional symptoms) was confirmed, and the patient was enrolled in the COMFORT-II trial at a starting dose of ruxolitinib 15 mg bid (platelet count at baseline: $138 \times 10^9/L$). The initial hemoglobin level was 140 g/L, and the white blood cell count was $15.6 \times 10^9/L$. At screening, the patient was found to be JAK2 V617F–positive. Cytogenetic analysis showed an additional abnormality of 46,XY,der(22)t(1;22)(q21;p11.2) [4]/46,XY[3]; the abnormal clone was detected in 4 out of 7 cells analyzed by G-banding, with an unbalanced translocation between chromosomes 1 and 22 that resulted in partial trisomy 1q—a recognized finding in MF.

After the initiation of ruxolitinib treatment, splenomegaly improved dramatically (Figure 1)—a 30% reduction in palpable spleen length was observed at week 4 (the first spleen assessment). However, the patient became mildly thrombocytopenic (Figure 2) with a platelet count of $86 \times 10^9/L$, and the dose was reduced to 10 mg bid as per study protocol. Platelet counts recovered with dose reduction, and the patient has remained on treatment at a dose of 10 mg bid. At this dose, splenomegaly progressively resolved. The smallest palpable spleen length measurement, 2 cm (a 90% reduction from baseline), was recorded after 108 weeks of ruxolitinib treatment. The patient was classified as having a spleen response, as defined per protocol, with a 42% reduction in spleen volume at week 24, a 58% reduction at week 48, and a 75% reduction at the latest assessment by MRI at week 144 (Figure 3). In terms of symptoms, both fatigue and intractable pruritus were present at study entry; within 48 hours of the initiation of ruxolitinib treatment, the pruritus had resolved (and has remained negligible) and the fatigue had improved markedly.

After 168 weeks of ruxolitinib treatment, morphologic analysis of the bone marrow indicated a significant improvement (Figure 4). At the prettrial baseline assessment in 2009, analysis of hematoxylin and eosin–stained trephine core sections showed maximally increased cellularity with disordered hematopoiesis and pleomorphic megakaryocytes (Mks), most of which were large and had abnormally lobated nuclei. Many formed tight clusters, and CD61 immunohistochemical analysis (highlighting Mks and platelets)
emphasized the increase, pleomorphism, and clustering. There was a diffuse and dense increase in reticulin with extensive intersections (Gomori reticulin stain) and focal formation of collagen (Martius Scarlet Blue trichrome stain), but no osteosclerosis (overall World Health Organization [WHO] score: 3). After 48 weeks of ruxolitinib treatment, these abnormalities were still apparent, cellularity decreased, and reticulin fibers were less prominent; however, patches of dense reticulin remained with extensive intersections. After longer treatment durations (168 weeks), hematoxylin and eosin staining showed normal overall cellularity and more uniformly dispersed MKs (best seen with CD61 immunostaining). Occasional atypical MKs were still present, but clustering was minimal and most MKs had normal morphologic characteristics. CD61 immunostaining confirmed that MKs were more dispersed, were not present in tight clusters, and had limited pleomorphism; platelet shedding into the marrow interstitium was minimal compared with baseline. Silver staining showed complete normalization of the fiber pattern (WHO score: 0), and only normal perivascular collagen was evident with Martius Scarlet Blue staining. In parallel with this, the red cell changes characteristic of myelofibrosis (teardrop polikilocytes and nucleated red cells) have also resolved, and the LDH normalized as documented in centrally reviewed laboratory findings.

Of interest, JAK2 V617F allele burden was much reduced with ruxolitinib treatment: from an absolute allele burden of 91% at baseline to approximately 11% at week 156—an 88% reduction. This reduction occurred gradually over the course of treatment (Figure 1). The cytogenetic abnormality persisted despite the resolution of fibrosis.

Ruxolitinib treatment was generally well tolerated by this patient. Hematologic adverse events (AEs) included thrombocytopenia, which resolved after dose reduction and anemia. These AEs are expected in the context of JAK1/JAK2 inhibitor therapy, but experience from the COMFORT studies has shown that they are manageable in most patients, and the incidence decreases after 6 months of treatment.9 There was a gradual decline in hemoglobin levels, from 140 g/L at baseline to 96 g/L at day 78. However, levels recovered shortly thereafter to ≥ 108 g/L for the remainder of treatment (Figure 2); the patient has not required any transfusions. Nonhematologic AEs included two lower respiratory tract infections (on study days 112 and 826) that resolved with antibiotic treatment. Other AEs of interest that were considered unrelated or unlikely to be related to treatment included basal cell carcinoma (resolved with Moh surgery) and squamous cell carcinoma (resolved with excision of the lesion on the right side of the chest).

Discussion

Dysregulation of the JAK/STAT pathway is a hallmark of MF,10,11 and the resulting overexpression of several pro-inflammatory cytokines has been implicated in the progression of fibrosis.12 Given the reported effects of ruxolitinib treatment on various pro-inflammatory cytokines,6,13,14 one might expect an improvement in bone marrow fibrosis in some patients. At the time of the primary analyses of the COMFORT studies, no major changes in the morphologic characteristics of bone marrow were observed (after 6 months and 1 year of treatment in COMFORT-I and -II, respectively).6,13 Reduced-intensity AHSC results have been shown to resolve fibrosis within 6 to 12 months in patients with MF15; a longer treatment duration may be necessary to observe significant improvements in fibrosis in the context of JAK1/JAK2 inhibitor therapy, where the pathway cannot be completely repressed. For example, in one retrospective analysis of patients at the MD Anderson Cancer Center receiving ruxolitinib in the phase I/II study, 15% of patients (10/67) had an improvement in fibrosis at 24 months and 24% (4/17) had an improvement at 48 months (assessed histologically on the basis of WHO fibrosis scoring). For comparison, 10% of patients (3/31) in a control group who received HC showed an improvement after 24 months, and no patients (0/20) showed an improvement at 48 months.16 Of note, in that analysis, 53% of ruxolitinib-treated patients showed stabilization in morphologic characteristics of bone marrow at 48 months compared with
35% of HC-treated patients. Published literature on interferon therapy is also notable for occasional reports of resolution of histopathological features in either PV (as documented in 3 patients by Larsen and colleagues17) or myelofibrosis; Silver and colleagues18 reported morphological remission in 2 of 17 patients with early MF (WHO grade 1 or 2 fibrosis and IPSS low or intermediate 1 at diagnosis). A large French group19 collated data regarding responses to interferon in myelofibrosis but did not document histological responses.

Here, we report for the first time the resolution of bone marrow fibrosis with normalization of hematopoiesis in a patient receiving ruxolitinib treatment in COMFORT-II, a pre-requisite for these studies was the presence of advanced disease (IPSS score intermediate 2 or above). The COMFORT studies have shown that ruxolitinib prolongs survival in patients with MF compared with placebo and best available therapy, which suggests a potential disease-modifying effect.9,20 Longer-term follow up of the COMFORT study cohorts should help to determine whether ruxolitinib treatment can indeed improve the morphologic characteristics of bone marrow for other patients with MF and affect the natural course of the disease; if it does, it will be of great interest to define what the particular characteristics of such responding patients might be.
Authorship: BSW and CNH are responsible for the integrity of the work, as a whole. BSW, DR, CK and CNH interpreted the data and prepared the text. BSW and CNH collected the images and generated the figures. All authors collected the data and approved the manuscript.

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References


Figure Legends

Figure 1. Ruxolitinib dose, palpable spleen length, and JAK2 V617F allele burden over time. bid, twice daily.

Figure 2. Platelet and hemoglobin levels over time.

Figure 3. Percentage change from baseline in spleen volume over time.

Figure 4. Histologic characteristics of bone marrow at baseline and after 48 and 168 weeks of ruxolitinib treatment (a full description is provided in the text). H&E, hematoxylin and eosin.
The graph illustrates the changes in spleen length (cm below the costal margin) and JAK2 V617F allele burden (%) over the study weeks. The red line represents the Ruxolitinib dose (mg bid), the blue line shows the spleen length, and the green line denotes the JAK2 V617F allele burden. The x-axis represents the study weeks, ranging from 0 to 168, and the y-axis for the spleen length is from 0 to 30, while the y-axis for the JAK2 V617F allele burden is from 0 to 100.