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TO THE EDITOR:

Efficacy and safety of ruxolitinib in regularly transfused patients with thalassemia: results from a phase 2a study

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Ineffective erythropoiesis is a key pathological feature in thalassemia and is the major perpetrator of profound anemia and hypoxia seen in these patients.[1-3] The inadequate tissue oxygenation in thalassemia sets up several compensatory mechanisms, including an increase in levels of erythropoietin (EPO), which is a principal regulator of both basal and stress erythropoiesis.[3,4] Preclinical data from thalassemic mice showed that the reactive increase in EPO concentration and mitigation of apoptosis induce uncontrolled expansion of early erythroid progenitors that fail to differentiate and further perpetuate ineffective erythropoiesis.[5] A series of preclinical experiments conducted by Libani et al demonstrated that erythroid cells isolated from both thalassemic mice and humans showed upregulation of JAK2.[5] Additional results from this study revealed the presence of actively proliferating erythroid cells in the enlarged thalassemic spleen, and treatment with JAK2 inhibitor (TG101209) prevented proliferation of thalassemic erythroid cells and reduced splenomegaly.[5] These findings suggest that treatment with ruxolitinib, a JAK1/JAK2 inhibitor, might benefit patients with thalassemia.

The Trial of Ruxolitinib in Thalassemia was a single-arm, open-label, multicenter, phase 2a study that explored the efficacy and safety of ruxolitinib in regularly transfused patients with thalassemia and spleen enlargement. The study included a core treatment phase of 30 weeks and an extension phase for patients who were receiving benefit at the end of 30 weeks. The study inclusion and exclusion criteria, and dose adjustment criteria are elaborated in the supplemental appendix (available on the *Blood* Web site). The starting dose of ruxolitinib was 10 mg twice daily for all patients. The study was done in accordance with the principles of Good Clinical Practice, the Declaration of Helsinki, and all local regulations.

The primary end point was percentage change of red blood cells (RBCs) transfused between weeks 6 and 30 of study compared with the period of 24 weeks before the start of study drug. A change of >10% increase or decrease in the hematocrit-adjusted volume of RBC during the treatment from baseline on a scatterplot was chosen as a threshold to indicate worsening or improvement in the transfusion requirement. The secondary end points were change in spleen volume from baseline as measured by magnetic resonance imaging at weeks 12 and 30 evaluated by central review, change in spleen length from baseline over time as measured by palpation, and change in pretransfusion hemoglobin levels from baseline over time. Assessment of biomarkers of erythropoiesis and iron metabolism at baseline, week 12, and week 30 visits was an exploratory end point of study.

A total of 30 patients with transfusion-dependent thalassemia (TDT, 27 with β-thalassemia and 3 with hemoglobin E β-thalassemia) received ruxolitinib in the study. Patient baseline characteristics are summarized in supplemental Table 1. Twenty-six patients completed the core phase and 4 patients discontinued the study before the end of core phase. The reasons for discontinuations were adverse events (AEs; 2 patients), withdrawal of consent (1 patient), and patient/guardian decision (1 patient). Of the 26 patients who completed the core phase, 18 entered the extension phase of the study. In the extension phase, 14 patients completed the treatment duration and 4 patients discontinued the study.

Of 30 patients, 3 were excluded from the primary analysis because they discontinued the treatment with ruxolitinib before week 18 (protocol-defined threshold for exposure). A mean decrease of 5.9% (95% confidence interval, −14.7 to 2.8) in the transfusion requirement of hematocrit-adjusted volume of RBC was observed in patients while on treatment compared with baseline. Of the 27 patients (per protocol population), 12 showed a decrease, 7 showed an increase, and 8 showed no change in transfused hematocrit-adjusted RBC volume during the treatment as compared with baseline (Figure 1). In addition, a trend for improvement in the median pretransfusion hemoglobin levels was observed over time at each 6-week interval period (supplemental Figure 1).

At week 30, spleen size measurements by palpation were available for 24 patients. A consistent reduction in spleen size from baseline over time was observed in patients treated with ruxolitinib (Figure 2A). The median percentage of spleen volume reduction from baseline was 22.5% at week 12 (range, −44.3 to 34.5; n = 26) and 26.4% at week 30 (range, −64.3 to 8.5; n = 25). At week 30, 24 of 25 evaluable patients (with magnetic resonance imaging scans available) were able to achieve some degree of reduction in spleen volume (Figure 2B). At week 30, the mean fold increase of hepcidin level from baseline was

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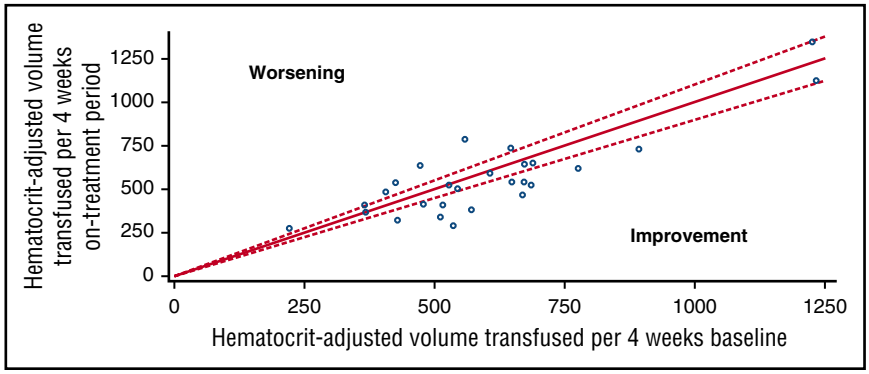
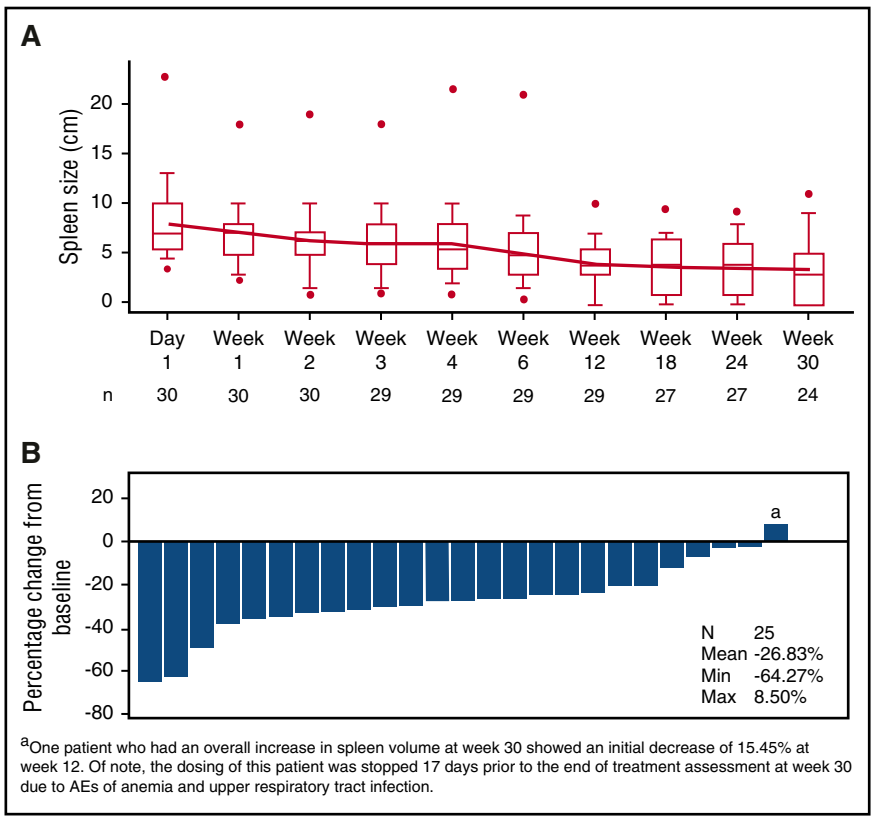


Figure 1. Scatter-plot of hematocrit-adjusted volume per 4 weeks at on treatment vs pretreatment periods. Each circle corresponds to 1 patient. The diagonal line indicates equal hematocrit-adjusted volume on treatment (weeks 6-30) and at baseline; dotted lines show 10% of decrease or increase.

1.7 (standard deviation [SD], 1.15; n = 24), whereas mean fold decreases of growth differentiation factor 15 and transferrin receptor levels from baseline were 0.8 (SD, 0.31; n = 24) and 0.670 (SD, 0.22; n = 24), respectively (supplemental Figure 2). Other biomarkers, such as serum iron, serum ferritin, transferrin, and transferrin saturation (%) reported very limited change from baseline.

Ruxolitinib was well tolerated in this study population, and the safety profile is consistent with the previous reports[6,7] (supplemental Table 2). The majority of AEs were primarily grade 1 or 2 in severity, with the exception of grade 3 or 4 anemia (16.7%). Serious AEs related to study drug included pneumonia (n = 1), viral pneumonia (n = 1), drug-induced hepatitis (n = 1), and pyrexia (n = 1). Only 2 patients discontinued the treatment because of AEs, both as a result of pyrexia (1 patient with viral pneumonia; 1 with *Staphylococcus aureus* bacteremia).

In our phase 2a study, although more patients had decreased transfused volume of RBC from baseline, there was no clinically relevant improvement in pretransfusion hemoglobin. One of the most interesting findings from our study is that ruxolitinib demonstrated a noticeable reduction in the spleen size over time in these patients with TDT. Except of 1 patient who was off study at week 30 because of AEs of anemia and upper respiratory tract infection, all patients were able to achieve at least some degree of spleen volume reduction with ruxolitinib treatment. This is consistent with the findings from a preclinical study by Casu et al reporting that short-term administration of JAK2 inhibitors reduces splenomegaly in mouse model of β-thalassemia.[8] In a TDT mice model, the administration of JAK2 inhibitors together with blood transfusion reduced spleen weight by 71% compared with transfusion alone.[8,9] Furthermore, flow cytometry studies revealed that the treatment with ruxolitinib led to a reduction in the number of erythroid progenitors in spleen



[a]One patient who had an overall increase in spleen volume at week 30 showed an initial decrease of 15.45% at week 12. Of note, the dosing of this patient was stopped 17 days prior to the end of treatment assessment at week 30 due to AEs of anemia and upper respiratory tract infection.

Figure 2. Spleen response in transfusion-dependent thalassemic patients treated with ruxolitinib. (A) Change in spleen length from baseline below the left costal margin over time. (B) Percent change in spleen volume from baseline at week 30 measured by magnetic resonance imaging. Max, maximum; min, minimum.

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compared with treatment with placebo.[5] These results show that ruxolitinib reduces splenomegaly in patients with thalassemia and suggest that targeting *EPO-EPOR-JAK2-STAT5* axis may limit the excessive proliferation of erythroid progenitors in spleen.

Although there was an increase in hepcidin levels with ruxolitinib treatment in our study, no significant changes in either serum iron or ferritin levels were observed over time. However, increased levels of hepcidin may suggest that the handling of iron absorption could be improved in the long term.

In conclusion, treatment with ruxolitinib in patients with TDT led to a sustained reduction in spleen size, and, hence, could be considered as an option for TDT patients with splenomegaly. Because the major purpose of reducing spleen size in patients with TDT is to improve pretransfusion hemoglobin and related reduction in transfusion needs where ruxolitinib had shown a limited effect, no further phase 3 studies are planned in regularly transfused patients with thalassemia.

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Authorship

Contribution: A.T.T. contributed to study design, data collection, and data interpretation and performed the research. Y.A., Z.K., E.C., A.M., A.K., and N.S. performed research and contributed to data collection and interpretation. S.R. contributed to study design and data interpretation. N.H. contributed to study design and performed statistical analyses. B.G., N.H., and B.M. contributed to data interpretation. All authors were involved in drafting the manuscript and approved the final version.

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Footnotes

The online version of this article contains a data supplement.

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TO THE EDITOR:

Histiocytic sarcoma: a population-based analysis of incidence, demographic disparities, and long-term outcomes

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Histiocytic sarcoma (HS) is a rare hematopoietic neoplasm derived from non-Langerhans histiocytic cells of the monocyte/macrophage system that is diagnosed using immunohistochemistry markers, such as CD68, lysozyme, CD4, and CD163, on the tissue biopsies.[1] HS can occur in isolation or in association with other hematological neoplasms like non-Hodgkin lymphoma (NHL), myelodysplasia, or acute leukemia.[2] HS has variable clinical presentation and outcomes, ranging from localized disease to multiple sites within a single system, to life-threatening disseminated disease (preferentially involving the skin, soft tissue, and gastrointestinal tract).