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Title: Ruxolitinib treatment improves muscle mass in patients with myelofibrosis

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Ethical statement: All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. The study was approved by the Institutional Review Boards.

Informed consent: Patients provided informed consent for molecular analyses.

Dear Editor,

Myelofibrosis is a Philadelphia-chromosome negative chronic myeloproliferative neoplasm characterized by development of bone marrow fibrosis, massive splenomegaly and life debilitating constitutional symptoms [1]. JAK inhibitor ruxolitinib has been approved for treatment of intermediate-2 and high risk myelofibrosis and is effective in reduction of splenomegaly and disease-related symptoms [2,3]. Due to specific reimbursement requirements, to continue ruxolitinib therapy after 6 months patients taking ruxolitinib in Croatia need to demonstrate either 30% reduction in the absolute spleen diameter (assessed by ultrasound) or 25% reduction in the spleen volume (assessed by computed-tomography (CT) or magnetic-resonance scans). Since 25% reduction in volume corresponds to 9% one-dimensional spleen reduction, patients obtaining CT scans are more likely to fulfil reimbursement requirements, providing a unique source of CT-measured data.

We retrospectively investigated psoas-muscles-area (PMA) at vertebra-L3 level from baseline and 6-months CT scans of myelofibrosis patients from two Croatian hematology centers that were treated with ruxolitinib due to high or intermediate-2 risk disease. Data for a total of 13 patients were available. PMA at 6 months was divided by baseline values to obtain percentage of PMA improvement. Since values were non-normally distributed, improvement in PMA was tested by paired Wilcoxon signed-rank test and non-parametric statistical tests (Mann Whitney U test, Spearman rank correlation, χ^2 test) were used to compare PMA ratio with clinical characteristics. MedCalc Statistical Software version 19.4.0 (MedCalc Software Ltd, Ostend, Belgium) was used.

Median age of analyzed cohort was 70 years, 6/13 (46%) were males. We observed statistically significant rise in PMA during 6 months ruxolitinib treatment (median PMA 1287 vs 1365; P=0.002) with majority of patients experiencing a modest rise in psoas muscle mass and only two patients experiencing a slight decline (among them one confined to the wheelchair due to earlier cervical spine injury) as shown in Figure 1A. Median PMA improvement after 6 months of ruxolitinib therapy was 6%. A total of 3/11 (23.1%) of patients experienced more than 10% improvement in PMA.

PMA improvement of 10% was associated with higher baseline hemoglobin level (median 117 vs 95 g/L; P=0.034) and lower International-Prognostic-Scoring-System (IPSS) score (2 vs 4; P=0.019) with all of patients achieving 10% PMA improvement belonging to the intermediate-2 IPSS group (100% vs 20% of patients with and without 10% PMA improvement; P=0.018; Figure 1B) and being non-transfusion dependent (100% vs 30% of patients with and without 10% PMA improvement; P=0.033). Improvement

in PMA was significantly correlated with decline in the longest spleen diameter (Rho=-0.57; P=0.042). PMA recovery was not significantly associated with etiology of myelofibrosis (primary vs secondary), degree of bone marrow fibrosis, *JAK2* V617F status, age, baseline CRP, absolute lymphocyte and albumin levels, nor with other disease characteristics (P>0.05 for all analyses). Although baseline and 6-months PMAs were significantly higher in males than in females, there was no significant difference in PMA dynamics between male and female patients (P=0.775).

To the best of our knowledge, our study is the first to provide evidence for muscle mass improvement during therapy with ruxolitinib. Patients with less advanced disease were more likely to achieve better PMA improvement favoring early start of ruxolitinib therapy. Direct mechanisms behind observed associations are yet to be established.

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Figure 1: A) Dynamics of psoas muscle area at vertebra L3 level during analyzed 6 months period. **B)** PMA improvement in patients with intermediate-2 and high risk disease as assessed by International Prognostic Scoring System.