A Case Report of Ruxolitinib Induced Hypocalcemia: A Stochastic or Deterministic Effect?

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Background

Ruxolitinib is a novel selective JAK 1/2 inhibitor approved for the treatment of myelofibrosis (MF) and polycythemia vera (PCV). Hypocalcemia associated with ruxolitinib has not been reported in early trials or in literature. It has a target specific action with JAK1/2 receptor and based on current evidence there is lack of interaction with JAK3 receptor which has a role in calcium homeostasis.

Case

A 65-year female presented with complaints of severe myalgia, fatigue, paresthesias of fingers and toes and a critical hypocalcemia. She has a history of CKD stage 3, PCV (since 1989), papillary thyroid carcinoma status post total thyroidectomy (1996), mild hypoparathyroidism (1996) from her thyroid surgery with associated hyperphosphatemia, which was managed successfully with phosphate binders for years. Her current blood work showed a corrected S. Ca 5.8 mg /dl (8.9-10.1 mg/dL) and ionised Ca 2.9 mg/dl (4.5 - 5.4 mg/dL). Other labs showed stable creatinine 1.5 mg/dl, intact PTH 29 pg/ml (14-72pg/ml) and 25,OH vitamin D level 35ng/ml (30-100ng/ml). She was diagnosed with PCV in 1989 and her peripheral blood counts were adequately controlled with intermittent phlebotomies and hydroxyurea up until 4 months ago. She was started on ruxolitinib 4 months ago due to progressive elevation of WBC and platelet counts above 40 x 10³ cells/ mm³ and 1.5 million cells/ mm³ respectively.

Discussion

The JAK family comprises of a group of tyrosine kinases JAK1, JAK2, JAK3 and TYK2. The JAK family plays a vital role in maintaining normal hematopoietic function. Ruxolitinib has a target specific action on JAK1/2 receptor and currently there is no evidence to suggest JAK3 receptor interaction.1-3 The temporal relation of ruxolitinib initiation to the drop in counts and hypocalcemia was evident in our case. Once drug was discontinued, hypocalcemia persisted for 4 weeks until calcium replacement initiated. There is only one reported case of hypocalcemia after ruxolitinib initiation where patient presented with tumor lysis, acute renal failure and hyperphosphatemia. Tumor lysis improved with expectant management however hypocalcemia persisted.4 Interestingly the JAK pathway is associated with Calcium homeostasis, phosphate and Vitamin D metabolism. Studies have shown JAK3 deficiency is associated with increase in 1,25 OH-D3 with resultant increase in intestinal phosphate absorption and inhibition of PTH production.4,5 Our patient had hypoparathyroidism and the resultant hyperphosphatemia was managed with phosphate binders and maintained stable with in normal value for many years. With ruxolitinib, it is unclear if there can be heightened sensitiveness to JAK3 receptor inhibition in specific population with concomitant parathyroid abnormalities. Another hypothesis is the interaction of JAK- STAT pathway with EGFR and PDGFR which play a role in osteoblast differentiation and fracture repair respectively. The exact role of such interactions at present is intangible and would require further studies.

The case highlights a unique association of ruxolitinib to hypocalcemia. It is yet to be proven whether this was a chance occurrence or a direct causal effect, however it is important to keep this association in mind since ruxolitinib is increasingly being used for myelofibrosis and polycythemia patients.

Table 1. Laboratory Results

<table>
<thead>
<tr>
<th>Lab</th>
<th>Jan 2015</th>
<th>Ruxolitinib 4 months ago</th>
<th>4/15/15</th>
<th>4/22/15</th>
<th>5/15/15</th>
</tr>
</thead>
<tbody>
<tr>
<td>S.Ca (9.6-10.6 mg/dL)</td>
<td>8.2</td>
<td>S</td>
<td>6.0</td>
<td>5.3</td>
<td>&lt;5</td>
</tr>
<tr>
<td>S.Phos (2.5-4.5 mg/dL)</td>
<td>4.1</td>
<td>T</td>
<td>7.1</td>
<td>3.9</td>
<td></td>
</tr>
<tr>
<td>Hb (12.1 - 14.5 g/dL)</td>
<td>11.6</td>
<td>A</td>
<td>8.5</td>
<td>9.7</td>
<td>10.4</td>
</tr>
<tr>
<td>Hct</td>
<td>38.5</td>
<td>R</td>
<td>26.9</td>
<td>31.6</td>
<td>32.8</td>
</tr>
<tr>
<td>WBCx10³ cell/mm³ (4.5-10)</td>
<td>50.1</td>
<td>E</td>
<td>11.5</td>
<td>17.0</td>
<td>21.9</td>
</tr>
<tr>
<td>Plateletsx10³ cell/mm³ (150-350)</td>
<td>733</td>
<td>D</td>
<td>244</td>
<td>779</td>
<td>714</td>
</tr>
</tbody>
</table>

References: