Platelet Kinetics in Idiopathic Thrombocytopenic Purpura Patients Treated with Thrombopoietin Receptor Agonists

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Keywords
Platelet survival · Platelet kinetics · Thrombopoietin · Romiplostim · Eltrombopag

Summary
Aim: Thrombopoietin receptor agonists (Tpo RA) increase platelet counts in the majority of chronic autoimmune thrombocytopenia (idiopathic thrombocytopenic purpura; ITP) patients. It is unknown whether this treatment may also improve platelet survival (PS) in these patients. \textbf{Methods:} In order to determine platelet survival (PS), autologous platelets were labeled with $^{111}$In oxine and retransfused in six patients under treatment with Tpo RA (romiplostim $n = 3$; eltrombopag $n = 3$). \textbf{Results:} Stable platelet counts of greater than $100 \times 10^3/\mu l$ were observed in all 6 patients. Platelet survival was decreased in all cases (mean 2.10 days; range 0.13–3.73 days). No correlation was found between platelet count and PS. Similarly, there was no significant relationship between platelet turnover and platelet count. However, a high platelet turnover, exceeding 25 or three times the norm was observed in 2 patients who presented the lowest PS (0.13 or 0.83 days). Two patients had a moderately shortened PS (1.91 or 2.42 days), and, correspondingly, a moderately increased platelet turnover rate (63,072 or 72,872 platelets/\mu l/day). \textbf{Conclusion:} These results indicate that Tpo RA may not only overcompensate platelet destruction in ITP, but may interfere with other mechanisms, which, in some cases, results in a reduced platelet destruction rate.

Schlüsselwörter
Thrombozytenüberleben · Thrombozytenkinetik · Thrombopoietin · Romiplostim · Eltrombopag

Zusammenfassung
Introduction

Chronic autoimmune thrombocytopenia (idiopathic thrombocytopenic purpura; ITP) is characterized by a reduced platelet count, antibody-mediated platelet destruction, and a significant decrease in platelet survival (PS). Impaired platelet production and T-cell-mediated platelet destruction has been implicated as playing a potential role [1]. Approximately 40% of patients with ITP display a reduced platelet turnover [2], and megakaryocytes are often decreased and/or damaged [3–5]. It has also been demonstrated that ITP patients have normal or only slightly increased levels of thrombopoietin (Tpo) [6, 7]. Furthermore, studies with thrombopoietin receptor agonists (Tpo RA) have demonstrated a dose-dependent response with a significant increase in platelets in almost 80% of patients treated for ITP. This platelet increase is not predictable or dose-dependent and varies amongst patients [8, 9].

A recent study demonstrated that Tpo RA resulted in the improvement of regulatory T-cell activity in ITP patients [10]. All these findings indicate that the effect of Tpo RA in ITP might not solely be explained by an increased platelet production that overcompensates platelet destruction. To further elucidate this, platelet kinetics were measured in 6 ITP patients treated with Tpo RA.

Patients and Methods

We evaluated the treatment course of 6 patients (age range, 55–82 years) with chronic ITP (splenectomized n = 3; non-splenectomized n = 3). Diagnosis of ITP was made according to established guidelines [11, 12].

Table 1. Characteristics of treated patients

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Age, years</th>
<th>Sex</th>
<th>Disease, years</th>
<th>Previous treatment</th>
<th>Ettrombopag, mg/day</th>
<th>Romiplostim, μg/kg/week</th>
<th>Platelets prior to Tpo-R-Mimetics × 10⁹/l</th>
<th>Duration of treatment with Tpo-R-Mimetics, days</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>73</td>
<td>M</td>
<td>&gt;5</td>
<td>PRED, IVIg, anti-D</td>
<td>75</td>
<td>19</td>
<td>152</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>80</td>
<td>F</td>
<td>12</td>
<td>PRED, IVIg</td>
<td>50</td>
<td>16</td>
<td>138</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>57</td>
<td>F</td>
<td>2</td>
<td>PRED, IVIg, CsA, Splx</td>
<td>25 twice weekly</td>
<td>14</td>
<td>125</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>70</td>
<td>M</td>
<td>5</td>
<td>PRED, MYCO, Splx</td>
<td>1</td>
<td>9</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>81</td>
<td>F</td>
<td>5</td>
<td>PRED, IVIg, Aza, Splx</td>
<td>3</td>
<td>6</td>
<td>43</td>
<td></td>
</tr>
<tr>
<td>6*</td>
<td>55</td>
<td>F</td>
<td>&gt;20</td>
<td>PRED, Aza</td>
<td>3</td>
<td>13</td>
<td>30</td>
<td></td>
</tr>
</tbody>
</table>

*Patient with Evans syndrome (autoimmune hemolytic anemia and autoimmune thrombocytopenia.

Table 2. Results of ¹¹¹In platelet kinetics

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Platelets at measurement × 10⁹/l</th>
<th>platelet half-life, h</th>
<th>Recovery, %</th>
<th>Survival, days</th>
<th>Turnover, platelets/μl/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>158</td>
<td>3.1</td>
<td>94.40</td>
<td>0.13</td>
<td>1,107,398</td>
</tr>
<tr>
<td>2</td>
<td>131</td>
<td>89.5</td>
<td>90.75</td>
<td>3.73</td>
<td>34,830</td>
</tr>
<tr>
<td>3</td>
<td>226</td>
<td>60.9</td>
<td>94.50</td>
<td>3.60</td>
<td>57,025</td>
</tr>
<tr>
<td>4</td>
<td>138</td>
<td>40.9</td>
<td>93.80</td>
<td>1.91</td>
<td>63,072</td>
</tr>
<tr>
<td>5</td>
<td>125</td>
<td>47.7</td>
<td>83.50</td>
<td>0.83</td>
<td>180,362</td>
</tr>
<tr>
<td>6</td>
<td>176</td>
<td>58.0</td>
<td>81.60</td>
<td>2.42</td>
<td>72,872</td>
</tr>
</tbody>
</table>

Results

Although platelet counts were observed to be greater than 100 × 10⁹/l, PS was reduced in all patients, ranging between 0.13 and 3.73 days (table 2). In correspondence to the latter finding, platelet turnover increased to more than 25 times the normal rate in 1 patient presenting the lowest PS (no. 1), and to a lesser degree in 3 other patients (no. 4, 5, and 6). No significant correlation between PS and platelet count or PS and platelet turnover was observed (fig. 1, 2). Based on normal values from previous studies (see discussion), PS may have
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moderately been increased or did not significantly change in the remaining 2 patients (no. 2 and 3). During observation of more than 2 years, continuous treatment with Tpo RA ensured ‘safe’ platelet counts in these patients.

**Discussion**

Previous studies have revealed a normal PS to be 7–10 days, whereby platelet turnover rates ranged between 40,000 to 60,000 platelets/nl/day. In ITP, a significantly decreased PS of several days or even hours has been observed. There was no clear correlation between platelet count and PS. Of extreme interest was the finding that increased platelet production was observed in approximately one third of ITP patients, whereas one third presented a decrease in platelet production [16, 17].

Though numerous therapies are useful in the treatment of ITP, only several studies have addressed platelet kinetics in treated patients. These studies revealed varying results, which included no change, increase, decrease, or normalization of platelet turnover following treatment with corticosteroids and splenectomy [18–24]. This is not surprising as several other factors are involved in the pathogenesis of ITP and may influence therapeutic effects. These include the concentration of endogenous Tpo, concentration and affinity of platelet autoantibodies, capability of macrophages to recognize and eliminate platelets from the circulation, and platelet production. Since any change of one or more factors may influence all findings in ITP, it is not surprising that the results obtained from different studies are different. This is supported by our findings in the present study. Prior to treatment with Tpo RA, all 6 patients presented with severe ITP, with platelet counts below $20 \times 10^9/\text{l}$. Platelet counts increased to greater than $100 \times 10^9/\text{l}$ in all patients post treatment. However, platelet counts were not found to correlate with PS, and platelet turnover remained variable among the patients. Although patients who demonstrated the highest reduction in PS also exhibited the highest platelet turnover, no significant correlation was found with platelet counts or PS. Due to the fact that PS is known to be decreased in ITP patients, we were unable to justify the measurement of PS prior to treatment with Tpo RA. Thus, it remains unknown as to how these drugs alter platelet kinetics in ITP patients. However, there is evidence that the stable rise in platelet counts cannot be solely explained by an increase in platelet production which exceeds platelet destruction, at least in patients that demonstrated a

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**Fig. 1.** Correlation between PS and platelet turnover. No significant correlation was observed ($r = 0.739, p = 0.094$).

**Fig. 2.** Correlation between PS and platelet count. No significant correlation was observed ($r = 0.3450, p = 0.503$).
relatively normal platelet turnover. There are two possible explanations for this phenomenon. Macrophages have a diminished capability of destroying platelets in these patients when compared to patients with a higher turnover, resulting in their reduction due to the elimination of additional platelets, leading to increased PS. A similar phenomenon occurs in ITP patients following transfusion of high doses of platelets [25] and coating of autologous red blood cells with antibodies, i.e. anti-D [26]. Another factor leading to the normalization in platelet turnover is the direct effect of Tpo RA on regulatory T-cell activity. Further studies on larger cohorts and pre- and post-treatment analysis are required to further elucidate these mechanisms.

**Acknowledgement**

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O.M. treated the patients, planned the study, analyzed the data and wrote the manuscript; E.H. performed the platelet kinetics and analyzed the data; A.S. planned the study, analyzed the data, and wrote the manuscript.

**Disclosure Statement**

A.S. and O.M. conduct clinical studies on behalf of Amgen and Glaxo-SmithKline and received consultation fees from Amgen and Glaxo-Smith-Kline. E.H. declares no conflict of interest.

**References**