Evaluation of AMG 531 Efficacy in Splenectomized Patients with Chronic ITP in a Randomized Placebo-Controlled Phase 3 Study

Plenary Session at ASH 2007
Presented by Terry B. Gernsheimer

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Hematology Grand Rounds
Friday, Jan 11, 2008
• Harrington et al, 1951
  - Normal patients infused with plasma from ITP patients will have drop in platelets

• Proposed mechanisms:
  - Autoantibodies to platelet membrane antigens
  - Accelerated clearance (Fcy receptor)
  - T-cell dysregulation

• Common treatments are aimed at modulation of immune system:
  - Steroid, IVIg, anti-D and splenectomy act primarily by interfering with platelet destruction
  - Other immunomodulatory agents suppress production of antiplatelet antibodies

• 20% of patients will be refractory to first-line therapy
• Over 1/3 will relapse following initial response
• Evidence that platelet production is suboptimal in large proportion of patients with ITP
  – In vitro studies showing reduced megakaryocyte production and impaired maturation in presence of some ITP plasmas
  → Autoantibody-induced suppression of megakaryopoiesis

• Suggests a strategy to increase platelet production may be effective
Megakaryopoiesis and thrombopoiesis are controlled by signaling through TPO binding to c-Mpl receptor.
• Recombinant protein ("peptibody") that induced thrombopoiesis by stimulating the TPO receptor

• Administered by subcutaneous injection

• An alternative to historically implemented immunomodulatory therapy
  – Designed to increase the production of platelets at a rate that outpaces destruction by immune system
• Carrier Fc domain and a peptide-containing domain that binds TPO receptor → Stimulates megakaryopoiesis

• No sequence homology with human TPO, therefore unlikely to cause anti-TPO antibodies (vs. PEG-MGDF)

• In healthy volunteers it resulted in increased platelet production/counts and did not induce neutralizing or cross-reacting antibodies against TPO
Phase 1-2 Clinical Trials

• In USA (Bussel, NEJM 2006) and Europe (Newland, Br J Haem 2006)
  – Patients with chronic ITP
  – Intervention:
    • Phase 1: Escalating-dose cohorts
    • Phase 2: AMG 531 vs. placebo
  – Majority achieved platelet count of $>50 \times 10^9/L$
  – No anti-TPO antibodies
  – No severe side effects at Phase 2 doses
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• Randomized, double-blind, placebo-controlled Phase 3 study

• Subcutaneous AMG 531 or placebo administered weekly for 24 weeks

• Eligibility criteria:
  – ≥ 18 yrs old
  – Chronic ITP
  – Prior splenectomy
  – Mean of three platelet counts ≤30x10^9/L over 8 days
  – Allowed to be on stable doses of azathioprine, danazol, etc.
• **Primary endpoint:**
  - **Durable platelet response**
    - Platelet count $\geq 50 \times 10^9$/L for $\geq 6$ during the last 8 weeks on therapy
    - No rescue medications during 24 weeks

• **Secondary endpoint:**
  - Safety
  - Decreased need for other therapies
• 2:1 randomization
• Starting dose: 1 mcg/kg
• Adjusted to maintain target platelet count 50-200x10^9/L (dosing algorithm used)
• ↓ other therapies if platelets >100
• Rescue medications allowed
• Follow-up to 36 weeks
63 patients meeting eligibility criteria

21 placebo
- 12 discontinued
- 2 died

42 treatment
- 2 discontinued due to A/E
  - 1 re-started
  - 1 did not re-start
  - 1 withdrawal of consent
- 2 died
Baseline Characteristics

• Median age: 52 yrs (range 26-88)

• Mean baseline platelet count: 14.7x10⁹/L

• Mean prior therapies: 5-6 (range 3-10)
## Results

<table>
<thead>
<tr>
<th></th>
<th>Patients on AMG 531</th>
<th>Patients on Placebo</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Durable platelet response</strong></td>
<td>16/24 patients (38%)</td>
<td>0/21 patients (0%)</td>
<td>--</td>
</tr>
<tr>
<td><strong>Overall response</strong></td>
<td>33/42 patients (79%)</td>
<td>0/21 patients (0%)</td>
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<tr>
<td><strong>Mean # of weeks with platelet response</strong></td>
<td>8 weeks</td>
<td>0 weeks</td>
<td>--</td>
</tr>
<tr>
<td><strong>Mean # of weekly platelet responses</strong></td>
<td>12.3/24 weeks (51%)</td>
<td>0.2/24 weeks (1%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Patients requiring rescue medications</strong></td>
<td>11/42 patients (26%)</td>
<td>12/21 patients (57%)</td>
<td>0.0175</td>
</tr>
<tr>
<td><strong>Concurrent meds discontinued or dose reduced by &gt;25%</strong></td>
<td>12/12 patients (100%)</td>
<td>1/6 patients (17%)</td>
<td>--</td>
</tr>
</tbody>
</table>
Results

- Common adverse events
  - Myalgias
  - Others...

- No discontinuation of trial medication due to common complaints

- Treatment-related adverse events (1 patient each):
  - Increased bone marrow reticulin – returned to baseline 3 months after stopping AMG 531
  - Popliteal embolism – patient had history of VTE; successfully treated, allowing study continuation

- Two deaths in placebo arm
- No therapy-related fatal events
• **Bleeding**
  - *This slide (conveniently?) flashed by quickly*
  - *I thought I might have seen more bleeding events in the treatment arm*
  - *Bleeding events are not reported in the abstract*

• **During question period:**
  - “Bleeding events occurred in both arms”
  - Possibly more severe events in placebo arm
“AMG 531 was well-tolerated, and effectively increased and sustained platelet counts in splenectomized patients with ITP.”

“AMG 531 patients required less frequent rescue medications in comparison to those receiving placebo, and were able to reduce their use of concurrent therapies.”
Comments/Questions

• Not clear how they dealt with drop outs in placebo arm (12 patients in total)

• Bleeding as an outcome

• Increased risk of thrombosis?

• Increased reticulin caused by drug → Possibility of progression to myelofibrosis?

• Risks of inducing myeloproliferative disorder? (TPO targets stem cells)
  – ?? Lower target platelet count (vs. 50-200)
<table>
<thead>
<tr>
<th>Table 1. Thrombopoietic growth factors</th>
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<tbody>
<tr>
<td><strong>First-generation thrombopoietic growth factors</strong></td>
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<tr>
<td>Recombinant human thrombopoietins</td>
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<tr>
<td>rhTPO</td>
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<tr>
<td>PEG-rHuMGDF</td>
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<tr>
<td>Recombinant TPO fusion proteins</td>
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<tr>
<td>Promegapoiietin (TPO/IL3 fusion protein)</td>
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<tr>
<td><strong>Second-generation thrombopoietic growth factors</strong></td>
</tr>
<tr>
<td>TPO peptide mimetics</td>
</tr>
<tr>
<td>Fab 59</td>
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<tr>
<td>AMG 531</td>
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<tr>
<td>Peg-TPOmp</td>
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<tr>
<td>TPO nonpeptide mimetics</td>
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<tr>
<td>Eltrombopag (SB497115, Promacta)</td>
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<tr>
<td>AKR-501</td>
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<tr>
<td>TPO agonist antibodies</td>
</tr>
<tr>
<td>Minibodies [VB22B sc(Fv)2]</td>
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<tr>
<td>Domain subclass-converted TPO agonist antibodies (MA01G4G344)</td>
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</tbody>
</table>

Kuter, Blood 2007
Thank you for listening!

Any questions?