Role of Thrombopoietin Receptor Agonists in Chronic and Refractory ITP

Gregory Cheng
Mechanism of ITP

- Traditionally immune thrombocytopenia (ITP) is thought to be a disease characterised by accelerated destruction of platelets by anti-platelet antibodies.
Mechanism of ITP

- Treatment is therefore primarily directed at reducing destruction of antibody-coated platelets
Economic Crisis

- Cut Budget
- Cut Jobs / Social benefits

Platelets Crisis

- Cut out the Spleen (Splenectomy)
Thrombopoietin (TPO) levels in ITP

- TPO levels are inappropriately low (near normal) in thrombocytopenic ITP patients


AMT=amegakaryocytic thrombocytopenia
Thrombopoietic Factors in ITP: Thrombopoietin Receptor (TPOr)-Targeted Therapy

- Stimulation of platelet production by TPO mimetics may be especially useful in patients not responsive to currently available treatment.
Eltrombopag (Revolade)

- Small molecule, non-peptide thrombopoietin receptor (TPO-R) agonist
- Dose-dependent increases in normally functioning platelets
- Does not prime platelet activation

MW = 564 Da

Stasi R, et al. Drugs 2008;68(7):901–12,
TPO-R agonists: mechanism of action

Eltrombopag

Inactive receptor

Active receptor

Thrombopoietin receptor

Signal transduction

Increased platelet production
Studies with Eltrombopag in Chronic ITP

- **Phase II/III:** Double-blind, placebo-controlled trials
  - 773A*: placebo or 30, 50, 75mg daily for 6 weeks
  - 773B: placebo or 50mg daily for 6 weeks

- **Phase II:** REPEAT – three cycles of 6 weeks each of active, open-label treatment

- **Phase III:** RAISE – double-blind, placebo-controlled trial for 6 months of variable doses of eltrombopag vs placebo in patients with or without splenectomy

- **Extension Study:** EXTEND (ongoing) open label safety and efficacy study of long-term daily treatment of subjects from Phase II–III

- **Phase IV:** (ongoing) open-label safety study to evaluate the long-term effect of eltrombopag on bone marrow reticulin and/or collagen fibers

*Supportive dose-finding studies – includes dose/schedule not licensed as per the SmPC

6. www.clinicaltrials.gov NCT01098487
Phase III Eltrombopag treatment of chronic ITP

Phase III (Part B) 6 weeks 2:1 randomisation

SoC + placebo (n=38)

SoC + 50mg eltrombopag (n=76)

N=114

TRA100773 B

p<0.001**
OR=9.61 (3.31, 27.86)

PBO 16%
50mg 59%

SoC=standard of care
2-sided p value; odds ratio (OR) eltrombopag / placebo

Eltrombopag: RAISE study

PHASE III RAAndomized Placebo-controlled ITP Study with Eltrombopag

Primary endpoint: odds of responding with a platelet count 50,000 to 400,000/µL during the 6-month treatment period

Screening

ITP patients, <30,000/µL

2:1

N=135

50mg eltrombopag + SoC

N=62

Placebo + SoC

6-month treatment period

Randomisation stratification:
- Splenectomy status
- Concomitant maintenance ITP therapy
- Baseline platelet counts ≤15 000/µL or >15 000/µL

SoC=standard of care

Patients in the eltrombopag group were 8 times more likely to respond compared with those in the placebo group \[\text{primary endpoint: odds ratio [99\% confidence interval 8.2 [3.59, 18.73]; } p<0.001\]  

Eltrombopag increases platelet counts and reduces bleeding.

Reduction in concomitant ITP therapy and rescue medication

Primarily a reduction in the use of corticosteroids

Mean change in SF-36v2 and FACT-Th6 scores

Significant improvements in some aspects of patient health-related quality of life: vitality (SF-36v2), less fatigue (FACIT) and the 6 items of FACT-Th6

EXTEND: open-label extension study

Chronic ITP patients previously enrolled in eltrombopag studies

Enrolled N=301

Eltrombopag dosing

Start 50mg

Dose modulated to platelet count

Stage 1: Eltrombopag dosing (≥100K)

Stage 2: Concomitant medication taper (≥50K)

Stage 3: Eltrombopag titration (≥50K)

Stage 4: Eltrombopag long-term safety + efficacy
EXTEND study: efficacy

- 88% (264/301) of patients achieved a response, i.e. platelet count $\geq 50,000/\mu L$
  - Response was similar irrespective of baseline platelet count, use of ITP medications and splenectomy status

### Hepatobiliary laboratory abnormalities (HBLA) across eltrombopag ITP trials

<table>
<thead>
<tr>
<th>HBLA type</th>
<th>RAISE N=135</th>
<th>EXTEND N=299</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, n(%)</td>
<td>17 (13)</td>
<td>24 (8)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>HBLA type</th>
<th>Median days to onset (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any HBLA</td>
<td>15 (1*-36)</td>
</tr>
<tr>
<td>ALT ≥3x ULN</td>
<td>8 (1-36)</td>
</tr>
<tr>
<td>AST ≥3x ULN</td>
<td>29 (15-29)</td>
</tr>
<tr>
<td>Bilirubin &gt;1.5x ULN</td>
<td>29 (15-29)</td>
</tr>
<tr>
<td>AP &gt;1.5x ULN</td>
<td>1 (1-33)</td>
</tr>
</tbody>
</table>

* A lower range of 1 indicates that patient had an enzyme value over the ULN at baseline

- The incidence of HBLAs meeting drug-induced liver injury screening criteria was low
- No pattern observed in median time to onset
- Most HBLAs were mild, reversible and without associated symptoms of impaired liver function

ALT=alanine aminotransferase, AP=alkaline phosphatase, AST=aspartate aminotransferase

Incidence of thromboembolic events (TEEs) across eltrombopag ITP trials

- 23 (5.1%) of 448 patients treated with eltrombopag experienced 30 TEEs
  - 5 patients experienced >1 TEE

<table>
<thead>
<tr>
<th>Event</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deep vein thrombosis</td>
<td>12</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>6</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>5</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>5</td>
</tr>
<tr>
<td>Transient ischemic attack</td>
<td>1</td>
</tr>
<tr>
<td>Prolonged reversible ischemic neurologic deficit</td>
<td>1</td>
</tr>
</tbody>
</table>

- 2 deaths (unrelated to TEE)
- No association observed with elevated platelet counts
## Incidence of TEEs in ITP

<table>
<thead>
<tr>
<th>Database</th>
<th>Patients with ITP</th>
<th>Patients without ITP</th>
</tr>
</thead>
<tbody>
<tr>
<td>US Claims Database 1</td>
<td>6.9% (197/2873)</td>
<td>3.4% (4027/116,933)</td>
</tr>
<tr>
<td>UK General Practice Research Database 2</td>
<td>6.1% (65/1070)</td>
<td>4.6% (197/4280)</td>
</tr>
</tbody>
</table>

- Limited epidemiologic data
- Incidence of TEEs seems to be higher in patients with ITP compared with patients without ITP

TEE risk factors

- All patients experiencing a TEE had $\geq 1$ risk factor for TEE
  - Hospitalisation without prophylactic anticoagulation, smoking, hypertension, oral contraceptive use, surgery for abdominal-pelvic malignancy, family history etc

- 15 patients with TEEs underwent genetic testing
  - 2/15 heterozygous for factor V Leiden mutation

- Median time to onset 229 days, range 1–981 days
- No relation with platelet counts

EXTEND study: bone marrow biopsies

- Over 180 on-treatment bone marrow biopsies performed in patients treated for >1 year

- 12 patients (8%) had reticulin grade MF-2 (no MF-3)
  - None had clinically relevant abnormalities in WBC or peripheral blood smear

39 Serial Biopsies showed no progression to MF grade 3 (one case of MF-1 to MF-2)
2 experienced a decrease in reticulin grade (MF-2 to MF-0 and MF-1 to MF-0)

Romiplostim (N-Plate)

- Fusion protein of Fc and TPO mimetic peptides
- No sequence homology with endogenous TPO
- Administered as weekly subcutaneous injections
  - Titrations between 1–10 µg/kg (adjustable based on platelet count)

Studies with Romiplostim in ITP

- **Phase I:** Open label study of 24 subjects treated in groups of 4 at six dose levels: 0.2, 0.5, 1.0, 3.0, 6.0, 10.0 µg/kg SQ
- **Phase II:** Double-blind, placebo-controlled trial of 1 or 3 µg/kg romiplostim (16 subjects) vs placebo (4 subjects)
- **Phase II:** Double-blind, placebo-controlled trial in 22 children on romiplostim and 5 placebo divided by age
- **Phase III:** Double-blind, placebo-controlled trial of romiplostim vs placebo in patients with or without splenectomy
- **Phase III:** Romiplostim vs standard of care in ITP with or without splenectomy
- **Extension Study (213):** Open label safety and efficacy study of long-term weekly treatment of subjects from Phase 1-3

# Romiplostim (N-Plate)

<table>
<thead>
<tr>
<th>Study ID-</th>
<th>Patients Design</th>
<th>duration (weeks)</th>
<th>dose (µg/kk BW)</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT0011147</td>
<td>Phase 1</td>
<td>6</td>
<td>0.2, 0.5, 1.0, 3.0, 6.0, 10.0</td>
<td>7/12 3-10 ug/kg responded</td>
</tr>
<tr>
<td>NCT0011147</td>
<td>Phase 2</td>
<td>6</td>
<td>1.0, 3.0, 6.0 once weekly</td>
<td>0/16 1-3 ug/kg responded</td>
</tr>
<tr>
<td>NCT00102323</td>
<td>Splenectomised</td>
<td>24</td>
<td>1.0 – 15.0 once weekly</td>
<td>79 vs 0% response</td>
</tr>
<tr>
<td>NCT00102336</td>
<td>Non-splenectomised</td>
<td>24</td>
<td>1.0 – 15.0 once weekly</td>
<td>88 vs 14% response</td>
</tr>
<tr>
<td>NCT00415592</td>
<td>vs SOC</td>
<td>52</td>
<td>3.0 – 15.0 once weekly</td>
<td>10 vs 30% failure</td>
</tr>
<tr>
<td>NCT00515203</td>
<td>Pediatric</td>
<td>12</td>
<td>1.0 – 5.0 once weekly</td>
<td>88% response</td>
</tr>
</tbody>
</table>

# Summary of TPOr agonist

<table>
<thead>
<tr>
<th></th>
<th>Eltrombopag (Revolade)</th>
<th>Romiplostinm (N-Plate)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Structure</strong></td>
<td>Non-peptide</td>
<td>peptide body</td>
</tr>
<tr>
<td><strong>Route of Administration</strong></td>
<td>Oral daily</td>
<td>sc weekly</td>
</tr>
<tr>
<td><strong>Onset of action</strong></td>
<td>1 week</td>
<td>1 to 2 weeks</td>
</tr>
<tr>
<td></td>
<td>Peak 2 weeks</td>
<td>peak 2 to 4 weeks</td>
</tr>
<tr>
<td><strong>Efficacy</strong></td>
<td>60-80%</td>
<td>60-80%</td>
</tr>
<tr>
<td><strong>Reduction of Concomitant ITP medication</strong></td>
<td>40-60%</td>
<td>40-60%</td>
</tr>
<tr>
<td><strong>Reduction of bleeding</strong></td>
<td>65-80%</td>
<td>60-80%</td>
</tr>
</tbody>
</table>
# Summary of TPOr agonist

- **Eltrombopag (Revolade)**
  - Thrombocytosis: Reversible
  - Thrombosis: 5.1%
  - Platelet activation: No
  - Autoantibody formation: No
  - Marrow fibrosis: 180 bx, no progression
  - Rebound thrombocytopenia: No

- **Romiplostim (N-Plate)**
  - Thrombocytosis: Reversible
  - Thrombosis: 5%
  - Platelet activation: No
  - Autoantibody formation: No
  - Marrow fibrosis: 12 bx, no progression
  - Rebound thrombocytopenia: No

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1. ANTI-ROMIPLOSTIM ANTIBODY

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Role of TPO-R agonists

- The most obvious patients would be chronic ITP splenectomised patients who are refractory to current treatments or those in whom splenectomy is contraindicated.
ASH guidelines: second-line treatment

ASH 2011 guidelines

Recommendation:
- Splenectomy if failed corticosteroids (1B)
- TPO-R agonists following relapse after splenectomy OR if splenectomy contraindicated and failed ≥1 other therapy (1B)

Suggestion:
- Eltrombopag and romiplostim for patients who have failed one therapy e.g. corticosteroids or IVIg and have not had a splenectomy (2C)*

*Licensed for second-line use where there is a contraindication for splenectomy (EMA)

LESS 30 x 10⁹/lits

ITP

Steroids/Dexamethasone

Fail

Splenectomy

Fail

Refused

Contraindicated

TPOr Agonist
Use of TPO-R agonists in ITP: questions…

- What dose should we start at and how quickly should we increase?
- Will different TPO-R agonists work in different patients?
- Are there additive effects/synergy with other treatments?
- Will TPO-R agonists be given indefinitely: will some patients go into remission?
- What will be the long term toxicity of continuous treatment?
Eltrombopag

- Once daily oral dose: 50mg
  - Adjusted between 25mg and 75mg as needed
  - AUC 70% to 80% higher in East Asian patients
  - Administered 4 hours before or after any calcium containing products or mineral supplements containing polyvalent cations
Revolade®: dose adjustments

- After initializing treatment with Revolade®, or after a dose alteration, no further changes to the dose should be made for at least 2 weeks.

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EXTEND

- 13 subjects – prolonged response off eltrombopag
- Median - 54.9 weeks
- Median time since diagnosis of ITP - 25.8 months (range 9-73 months)
- Median time on eltrombopag - 258 days (14-1107)
- 5 patients had splenectomy

EHA London 2012. poster 796
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Elevated Liver Enzymes
Long remission
Thromboembolism
Rebound thrombocytopenia
Ophthalmological
Myelofibrosis
Budget
Obstetrics
Pediatrics
Autoantibodies
Growing applications