CURRENT PERSPECTIVES ON THE TREATMENT OF PRIMARY CHRONIC ITP IN ADULTS

AN INDEPENDENT, CME-ACCREDITED SYMPOSIUM

14 July 2020
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• Each participant should claim only those hours of credit that have actually been spent in the educational activity.

*CME credit is only available for attendance during the live event
WELCOME AND INTRODUCTION

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DISCLOSURES

• **Research support:** Alexion, Alnylam, Baxalta, Bayer, CSL Behring, Ferring Pharmaceuticals, Novo Nordisk, Octapharma, Rigel Pharmaceuticals, Roche, Sanofi, Shire, Siemens, Sobi, Werfen

• **Stock ownership:** none
EDUCATIONAL OBJECTIVES

1. Review of the current standard of care in ITP, detailing its risk and benefit.
2. Explain the mechanism of action and clinical data of potential new and innovative therapeutic options in ITP.
3. Comparison of standard of care today and in the future.
Introduction

Evolution of Treatment in Chronic Primary ITP in Adults

Clinical Experience With TPO-RAs

Current Challenges and Novel Treatment Options in ITP

Summary

ITP, immune thrombocytopenia; TPO-RA, thrombopoietin receptor agonist
INTRODUCING THE FACULTY

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Poland

Prof David J. Kuter, MD, DPhil
United States

Prof Pål Andrè Holme, MD, PhD
Norway

Dr Vickie McDonald, MA, MRCP, FRCPath, PhD
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Professor of Haematology and Senior Haematologist at the Oslo University Hospital, Rikshospitalet, and Institute of Clinical Medicine, University of Oslo, Norway

Consultant Haematologist at the Royal London Hospital, UK; honorary senior lecturer at Queen Mary University of London; and National Chief Investigator for the UK ITP registry

ITP, immune thrombocytopenia
IMMUNE THROMBOCYTOPENIA (ITP)

Acquired autoimmune disorder characterised by a low platelet count resulting from platelet destruction and impaired platelet production.

Incidence 2–5 per 100,000

Isolated primary condition or secondary to other conditions (e.g. concomitant autoimmune disease)

Heterogeneous disorder – variable clinical symptoms (mild to severe bleeds)

Severe bleeding is reported in 9.5% of adults and 20.2% of children\(^1\)

Adults with ITP have a 1.3–2.2-fold higher mortality than the general population (due to cardiovascular disease, infection, and bleeding)\(^2\)

Significant impact on health-related quality of life (HRQoL) (e.g. fatigue is reported in 22–45% of patients with ITP)\(^1\)

Many patients with ITP may require special attention and long-term treatment\(^3,4\)

Optimal treatment decisions for each patient remain a challenge in many cases\(^3,4\)

ITP, immune thrombocytopenia
EVOLUTION OF TREATMENT IN ITP

PÅL ANDRÈ HOLME, MD, PhD
Professor of Haematology
Department of Haematology and
Institute of Clinical Medicine, Oslo University Hospital
University of Oslo, Norway

ITP, immune thrombocytopenia
WHAT ARE THE CURRENT TREATMENT OPTIONS FOR CHRONIC ITP IN ADULTS?
DISCLOSURES

• **Consultant:** Bayer, CSL, Novo Nordisk, Octapharma, Pfizer, Shire, Sobi
MANAGEMENT OF NEWLY DIAGNOSED ITP IN ADULTS WHO ARE ASYMPTOMATIC OR HAVE MINOR MUCOCUTANEOUS BLEEDING

**Treatment**

- **Platelet count ≥ 30 x 10⁹/L**
  - Observation

- **Platelet count < 30 x 10⁹/L**
  - Corticosteroids (without rituximab)
    - Prednisone (0.5–2.0 mg/kg per day) or dexamethasone (40 mg/day for 4 days) as initial therapy
    - Short course (≤ 6 weeks) of prednisone

**Admission or outpatient management**

- **Platelet count < 20 x 10⁹/L**
  - Hospital admission (in case of bleeds)

- **Platelet count ≥ 20 x 10⁹/L**
  - Outpatient management

ITP, immune thrombocytopenia
## ITP TREATMENT OPTIONS

<table>
<thead>
<tr>
<th>Clinical situation</th>
<th>Therapeutic option</th>
</tr>
</thead>
</table>
| **Initial treatment of newly diagnosed ITP** | **Corticosteroids**  
• dexamethasone  
• methylprednisolone  
• prednis(ol)one  
**Intravenous immunoglobulin (IVIg)**  
**Anti-D** (licensed and available for ITP in only a few countries) |
| **Subsequent treatment**                    | **Medical therapies with robust evidence**  
• rituximab  
• thrombopoietin receptor agonists (TPO-RAs: eltrombopag, avatrombopag, romiplostim)  
• fostamatinib  
**Medical therapies with less robust evidence**  
• azathioprine  
• cyclophosphamide  
• cyclosporine A  
• danazol  
• dapsone  
• mycophenolate mofetil  
• TPO-RA switch  
• vinca alkaloids  
**Surgical therapy**  
• Splenectomy |
| **Treatment after failure of multiple therapies** | **• Accessory splenectomy**  
• alemtuzumab  
• Combination of initial and subsequent therapies  
• Combination chemotherapy  
• Clinical trials  
• Haematopoietic stem cell transplantation  
• Splenectomy, if not already performed  
• Supportive care |

ITP, immune thrombocytopenia
RECOMMENDED ITP TREATMENT GOALS

Treatment goals should be individualised to the patient and the phase of the disease.

- Treatment should prevent severe bleeding episodes.
- Treatment should maintain a target platelet count > 20–30 x 10⁹/L.
- Treatment should have minimal toxicity.
- Treatment should optimise HRQoL.

At least for symptomatic patients, because the risk of major bleeding increases below this level.

HRQoL, health-related quality of life; ITP, immune thrombocytopenia
RECOMMENDED STRATEGY FOR SUBSEQUENT ITP THERAPY

• There are many medical treatment options with few adverse events (AEs)\(^1\)
  – Not all therapies are available in all countries
  – Therefore the recommendations should be modified on the basis of available resources and patient preference

• Some medical options may require continued treatment\(^1\)

• Up to 1/3 of patients may remit in 1 year and up to 80% may remit in 5 years\(^2\)
  – If possible, splenectomy should be deferred for ≥ 1 year to allow for remission

ITP, immune thrombocytopenia
ALGORITHM FOR THE SELECTION OF SECOND-LINE THERAPY IN ADULTS WITH ITP

Patient places a high value on achieving durable response
Patient places a high value on avoiding long-term medication

Primary treatment options: TPO-RA, rituximab

Assess patient values and preferences

3–12 months

Assess duration of ITP

> 12 months

Primary treatment options: rituximab, splenectomy, TPO-RA

Assess patient values and preferences

Patient places a high value on achieving durable response
Patient places a high value on avoiding long-term medication

TPO-RA

Patient places a high value on avoiding surgery
Patient places a high value on achieving durable response

Treatment options: splenectomy, TPO-RA

rituximab

Patient places a high value on avoiding surgery
Patient places a high value on achieving durable response

Treatment options: rituximab, splenectomy

TPO-RA

Patient places a high value on avoiding surgery
Patient places a high value on achieving durable response

Treatment options: rituximab, TPO-RA

rituximab

Selection of second-line therapy in adults with ITP should be individualised according to duration of disease and patient values and preferences. Other factors that may influence treatment decisions include frequency of bleeding sufficient to require hospitalisation or rescue medication, comorbidities, compliance, medical and social support networks, cost, and availability of treatments. Patient education and shared decision-making is encouraged.

ITP, immune thrombocytopenia; TPO-RA, thrombopoietin receptor agonist
THERAPEUTIC MECHANISMS OF CURRENT ITP TREATMENTS

ITP, immune thrombocytopenia; IVIg, intravenous immunoglobulin; Th, T helper (cell); TPO-RA, thrombopoietin receptor agonist
THERAPEUTIC MECHANISMS OF TPO-RAs

TPO-RAs may also have immunomodulatory effects with increased regulatory T- and B-cell effects.

AKT, a serine threonine protein kinase; cMPL, thrombopoietin receptor; ERK, extracellular-signal-regulated kinase; GRB2, growth factor receptor-binding protein 2; JAK, Janus kinase; MAPK, mitogen-activated protein kinase; PI3K, phosphatidyl-inositol 3-kinase; RAF, rapidly accelerated fibrosarcoma kinase; RAS, rat sarcoma GTPase; SHC, Src homology collagen protein; SOS, son of sevenless; STAT, signal transducer and activator of transcription; TPO-RA, thrombopoietin receptor agonist.

WHAT ARE THE KEY SAFETY AND EFFICACY DATA SUPPORTING THESE TREATMENT OPTIONS?
COMPELLING EVIDENCE OF PLATELET RESPONSE WITH TPO-RAs

OVERALL PLATELET RESPONSE IN RANDOMISED CONTROLLED TRIALS (RCTs) OF RITUXIMAB OR TPO-RAs

<table>
<thead>
<tr>
<th>Study</th>
<th>Notes</th>
<th># Response/Total (%)</th>
<th>Response ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Treated</td>
<td>Placebo/SOC</td>
</tr>
<tr>
<td>Eltrombopag v. Placebo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bussel et al (2007)</td>
<td>Non-splenectomized</td>
<td>30 mg</td>
<td>5/15 (33%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>50 mg</td>
<td>14/15 (93%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>75 mg</td>
<td>15/17 (88%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Splenectomized</td>
<td>30 mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>50 mg</td>
<td>8/15 (53%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>75 mg</td>
<td>8/11 (73%)</td>
</tr>
<tr>
<td>Bussel et al (2009)</td>
<td>Non-splenectomized and Splenectomized</td>
<td>43/73 (59%)</td>
<td>6/37 (16%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>48/73 (66%)</td>
<td>6/37 (24%)</td>
</tr>
<tr>
<td>Cheng et al (2011)</td>
<td>Non-splenectomized and Splenectomized</td>
<td>106/135 (79%)</td>
<td>17/61 (28%)</td>
</tr>
<tr>
<td>Tomiyama et al (2012)</td>
<td>Non-splenectomized and Splenectomized</td>
<td>9/15 (60%)</td>
<td>0/8 (0%)***</td>
</tr>
<tr>
<td>Rituximab v. Placebo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arnold et al (2012)</td>
<td>Non-splenectomized</td>
<td>20/32 (62%)</td>
<td>19/26 (73%)</td>
</tr>
<tr>
<td>Ghanima et al (2015)</td>
<td>Non-splenectomized</td>
<td>40/55 (73%)</td>
<td>36/54 (67%)</td>
</tr>
<tr>
<td>Romiplostim v. Placebo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bussel et al (2006)</td>
<td>Non-splenectomized and Splenectomized</td>
<td>1 µg/kg</td>
<td>7/8 (88%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3 µg/kg</td>
<td>3/8 (38%)</td>
</tr>
<tr>
<td></td>
<td>Splenectomized</td>
<td>33/42 (79%)</td>
<td>0/21 (0%)***</td>
</tr>
<tr>
<td>Kuter et al (2010)**</td>
<td>Non-splenectomized</td>
<td>127/138 (92%)</td>
<td>26/51 (51%)</td>
</tr>
<tr>
<td>Shirasugi et al (2011)</td>
<td>Non-splenectomized and Splenectomized</td>
<td>21/22 (95%)</td>
<td>1/12 (8%)</td>
</tr>
</tbody>
</table>

CI, confidence interval; SOC, standard of care; TPO-RA, thrombopoietin receptor agonist

# BLEEDING IN RCTs OF RITUXIMAB OR TPO-RAs

<table>
<thead>
<tr>
<th>Study</th>
<th>Notes</th>
<th># Bleed/Total (%)</th>
<th>Rate ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Treatment</td>
<td>Placebo/SOC</td>
</tr>
<tr>
<td><strong>Eltrombopag v. Placebo</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bussel et al (2007)</td>
<td>Non-splenectomized and Splenectomized</td>
<td>30 mg</td>
<td>5/29 (17%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>50 mg</td>
<td>2/27 (7%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>75 mg</td>
<td>1/26 (4%)</td>
</tr>
<tr>
<td>Bussel et al (2009)</td>
<td>Non-splenectomized and Splenectomized</td>
<td>7/76 (9%)</td>
<td>5/38 (13%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>20/51 (39%)</td>
<td>18/30 (60%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>46/76 (61%)</td>
<td>30/38 (79%)</td>
</tr>
<tr>
<td>Cheng et al (2011)</td>
<td>Non-splenectomized and Splenectomized</td>
<td>106/135 (79%)</td>
<td>56/60 (93%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>44/135 (33%)</td>
<td>32/60 (53%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>26/135 (19%)</td>
<td>19/61 (31%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1/135 (1%)</td>
<td>4/61 (7%)</td>
</tr>
<tr>
<td><strong>Rituximab v. Placebo</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arnold et al (2012)</td>
<td>Non-splenectomized</td>
<td>7/32 (22%)</td>
<td>6/26 (23%)</td>
</tr>
<tr>
<td>Ghanima et al (2015)</td>
<td>Non-splenectomized</td>
<td>19/55 (35%)</td>
<td>21/54 (39%)</td>
</tr>
<tr>
<td><strong>Romiplostim v. Placebo</strong></td>
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<td></td>
</tr>
<tr>
<td>Bussel et al (2006)</td>
<td>Non-splenectomized and Splenectomized</td>
<td>1 μg/kg</td>
<td>0/8(0%)**</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3 μg/kg</td>
<td>0/8(0%)**</td>
</tr>
<tr>
<td>Kuter et al (2008)</td>
<td>Non-splenectomized and Splenectomized</td>
<td>6/84 (7%)</td>
<td>5/41 (12%)</td>
</tr>
<tr>
<td>Kuter et al (2010)*</td>
<td>Non-splenectomized</td>
<td>20/154 (13%)</td>
<td>13/75 (17%)</td>
</tr>
<tr>
<td></td>
<td>Non-splenectomized</td>
<td>5/154 (3%)</td>
<td>5/75 (7%)</td>
</tr>
<tr>
<td>Shirasugi et al (2011)</td>
<td>Non-splenectomized and Splenectomized</td>
<td>8/22 (36%)</td>
<td>10/12 (83%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1/22 (5%)</td>
<td>1/12 (8%)</td>
</tr>
</tbody>
</table>

CI, confidence interval; RCT, randomised controlled trial; SOC, standard of care; TPO-RA, thrombopoietin receptor agonist

## AVATROMBOPAG SUPERIOR TO PLACEBO

### EFFICACY ENDPOINTS, PHASE 3 STUDY

<table>
<thead>
<tr>
<th></th>
<th>Avatrombopag (n = 32)</th>
<th>Placebo (n = 17)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median cumulative duration of platelet response, weeks (min., max.)*</td>
<td>12.4 (0, 25)</td>
<td>0.0 (0, 2)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Platelet count ≥ 50 x 10⁹/L at day 8, % (95% CI)</td>
<td>65.6 (49.2–82.1)</td>
<td>0.0</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Any bleeding event†, %</td>
<td>43.8</td>
<td>52.9</td>
<td>NS</td>
</tr>
</tbody>
</table>

*The total number of weeks in which platelet count is ≥ 50 x 10⁹/L during the core study in the absence of rescue therapy.

†Lower for avatrombopag when adjusted for the 2.6-fold longer mean exposure time for avatrombopag-treated patients.

CI, confidence interval; NS, not significant; SD, standard deviation

WHAT ARE THE MAIN UNMET NEEDS IN CHRONIC ITP IN ADULTS?
KEY UNMET NEEDS IN CHRONIC ITP

- When to introduce which treatment option
- Access
- Heterogenicity of the disease
- Need for a tailored treatment approach
- Optimal management of platelet fluctuations during treatment
- Risk and minimisation of risk of bleeding and thrombotic events

ITP, immune thrombocytopenia
No head-to-head RCTs have directly compared subsequent therapy.

More RCTs are needed.

How do we obtain better long-term results using rituximab?

The mechanisms of failure of TPO-RAs are not well known.

Who will have a durable response after TPO-RA discontinuation?

What are the long-term effects of TPO-RAs?
CLINICAL EXPERIENCE WITH TPO-RAs

David J. Kuter, MD, DPhil
Chief of Hematology, Massachusetts General Hospital
Professor of Medicine, Harvard Medical School

Vickie McDonald, MA, MRCP, FRCPath, PhD
Consultant Haematologist, Royal London Hospital
Honorary Senior Lecturer, Queen Mary University of London
GUIDELINES NOW SUGGEST STARTING TPO-RA s EARLIER IN THE COURSE OF THE DISEASE. WHAT DATA ON EARLY TPO-RA TREATMENT ARE AVAILABLE?

David J. Kuter

TPO-RA, thrombopoietin receptor agonist
DISCLOSURES

- **Research support:** Agios, Alnylam, Argenx, Bioverativ, Bristol Myers Squibb, Incyte, Principia, Protalix, Rigel, Syntimmune
- **Consulting:** Alnylam, Amgen, Argenx, 3Bios, Bristol Myers Squibb, Dova, Fujifilm, Genzyme, GSK, Kirin, Medimmune, ONO, Pfizer, Principia, Rigel, Shionogi, Syntimmune, UCB
- **Stock ownership:** Rubius
- **Off-label uses:** none
TPO-RAs are as effective in early ITP as in chronic ITP

ITP, immune thrombocytopenia; TPO-RA, thrombopoietin receptor agonist
EARLY ITP VS CHRONIC ITP

**Early**
- **Newly diagnosed**: 0–3 months
- **Persistent ITP**: > 3–12 months

**Chronic**
- Before 2009, > 6 months
- Basis for regulatory approval of romiplostim and eltrombopag
- > 1 year
- Chronic ITP: > 12 months

- No known pathophysiological difference
  - “Epitope walking”? 

- Concept of “chronic” deserves updating

ITP, immune thrombocytopenia
## POOLED ANALYSIS OF NINE STUDIES OF ROMIPLOSTIM

<table>
<thead>
<tr>
<th></th>
<th>ITP ≤ 1 year</th>
<th>ITP &gt; 1 year</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt; 3 months (n = 155)</td>
<td>3–12 months (n = 156)</td>
</tr>
<tr>
<td><strong>Female, n (%)</strong></td>
<td>77 (50)</td>
<td>88 (56)</td>
</tr>
<tr>
<td><strong>Age, median (Q1, Q3), years</strong></td>
<td>52 (32, 69)</td>
<td>52 (35, 68)</td>
</tr>
<tr>
<td><strong>Baseline platelet count, median (Q1, Q3), ( \times 10^9/L )</strong></td>
<td>15 (8, 27)</td>
<td>20 (12, 29)</td>
</tr>
<tr>
<td><strong>ITP duration, median (Q1, Q3), months</strong></td>
<td>1.2 (0.7, 2.0)</td>
<td>5.8 (4.2, 8.4)</td>
</tr>
<tr>
<td><strong>Prior therapies, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 3</td>
<td>104 (67)</td>
<td>98 (63)</td>
</tr>
<tr>
<td>&gt; 3</td>
<td>6 (4)</td>
<td>11 (7)</td>
</tr>
<tr>
<td>Not collected</td>
<td>45 (29)</td>
<td>47 (30)</td>
</tr>
<tr>
<td><strong>Prior splenectomy, n (%)</strong></td>
<td>6 (4)</td>
<td>19 (12)</td>
</tr>
</tbody>
</table>

ITP, immune thrombocytopenia; Q1, quartile 1; Q3, quartile 3
IDENTICAL FREQUENCIES OF PLATELET RESPONSE: ITP ≤ 1 YEAR VS > 1 YEAR

<table>
<thead>
<tr>
<th>Patients with platelet response (%)</th>
<th>ITP-romi ≤ 1 year (n = 277)</th>
<th>ITP-romi &gt; 1 year (n = 634)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response ≥ 75% of time</td>
<td>74%</td>
<td>71%</td>
</tr>
<tr>
<td>Response ≥ 90% of time</td>
<td>61%</td>
<td>56%</td>
</tr>
<tr>
<td>Durable response (≥ 6 weeks in weeks 17–24)</td>
<td>53%</td>
<td>49%</td>
</tr>
</tbody>
</table>

ITP-romi, patients with immune thrombocytopenia treated with romiplostim
**EARLY ITP: STUDY DESIGN**

**PHASE 2, INTERVENTIONAL, SINGLE-ARM STUDY**

**SCREENING**
- 12 months
  - **TREATMENT**
    - romiplostim 1–10 μg/kg to platelets ≥ 50 x 10⁹/L
    - Adjust to keep platelets 50–200 x 10⁹/L

**REMISSION EVALUATION**
- If platelet count ≥ 50 x 10⁹/L without any ITP Rx, patient enters remission evaluation
- Remission ≥ 24 weeks (platelets ≥ 50 x 10⁹/L) without any ITP Rx

**Remission ≥ 50 x 10⁹/L without any ITP Rx < 24 weeks**
- Follow in remission period (≤ 24 weeks)

**Remission ≥ 50 x 10⁹/L without any ITP Rx ≥ 24 weeks**
- Taper romiplostim dose

**Remission ≤ 20 x 10⁹/L < 4 weeks, 20–50 x 10⁹/L, or ITP Rx**
- Stabilisation period (optimise Rx before discontinuing study)

**Remission ≤ 20 x 10⁹/L ≥ 4 weeks, at max dose**
- End of study

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*a* For patients meeting these criteria in the treatment period, the 24 weeks would start then.

*b* If these criteria were met in the treatment period, treatment would be discontinued.

ITP, immune thrombocytopenia; Rx, therapy
## EARLY ITP: RESPONSES

<table>
<thead>
<tr>
<th></th>
<th>Romiplostim (n = 75)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with platelet response, a n (%)</td>
<td>70 (93)</td>
</tr>
<tr>
<td>Time to platelet response, median (95% CI), weeks</td>
<td>2.1 (1.1–3.0)</td>
</tr>
<tr>
<td>Patients with ITP remission b n (%)</td>
<td>24 (32) (22–44)</td>
</tr>
<tr>
<td>Time to ITP remission, b median (range), weeks</td>
<td>27 (6–57)</td>
</tr>
</tbody>
</table>

a Platelet response = median platelet count ≥ 50 x 10⁹/L during any month.
b Remission = all platelet counts ≥ 50 x 10⁹/L for ≥ 6 months without romiplostim or any ITP medication.
31 patients started ITP remission. Patients starting remission were followed for 6 months only.
**PLATELET COUNTS AND DOSING:**

**ALL PATIENTS**

- A platelet count ≥ 50 x 10⁹/L was achieved in 25% of patients after 1 week and in 50% after 2 weeks.
- Median (Q1, Q3) treatment duration was 51 (18, 52) weeks in a 12-month period; range 0.3–52.4 weeks.
- Median (Q1, Q3) average weekly dose was 2.6 (1.6, 3.9) μg/kg; range 0.7–9.0 μg/kg.

Q1, quartile 1; Q3, quartile 3

GUIDELINES

• In adults with ITP lasting $\geq$ 3 months who are corticosteroid-dependent or have no response to corticosteroids, the ASH guideline panel suggests¹
  – Either splenectomy or a TPO-RA
  – Rituximab rather than splenectomy
  – TPO-RA rather than rituximab

• In adults with persistent or chronic ITP after steroid cessation, the International Consensus Report² recommends medical therapy (TPO-RA, rituximab, fostamatinib) for 12–24 months before considering splenectomy

ASH, American Society of Hematology; ITP, immune thrombocytopenia; TPO-RA, thrombopoietin receptor agonist
Many ITP patients do not need treatment

Initial treatment is prednisone or IVIg

Splenectomy works

But increased rate of VTE, infection

Not all ITP in adults will become or remain chronic

Give medical therapy a chance before splenectomy

• rituximab occasionally gives a long-term treatment-free response
• TPO-RAs are highly effective
  • Low rate of AEs
  • Improve HRQoL
  • May not need to be “forever”
• fostamatinib may be considered
• Don’t forget danazol, azathioprine, dapsone, MMF, cyclosporine

AE, adverse event; HRQoL, health-related quality of life; ITP, immune thrombocytopenia; IVIg, intravenous immunoglobulin; MMF, mycophenolate mofetil; TPO-RA, thrombopoietin receptor agonist; VTE, venous thromboembolism
CHANGING TREATMENT PATTERNS IN ITP: WHERE ARE WE NOW?

Vickie McDonald
DISCLOSURES

- **Advisory and speaker work:** AbbVie, Amgen, Bayer, Novartis
**GOALS OF THERAPY IN ITP**

**Phase** | **Definition** | **Chance of spontaneous remission** | **Treatment goal**
--- | --- | --- | ---
New diagnosis, acute | Up to 3 months after diagnosis | Common | Stop bleeding
Prevent bleeding
Rapid platelet count rise
Prevent bleeding
Cure?
Persistent | 3–12 months after diagnosis | Less common | Stop or prevent bleeding
Stabilise platelet count
Mindful of AEs from medication
Cure?
Chronic | > 12 months from diagnosis | Uncommon | Prevent bleeding
Mindful of AEs from medication

**Optimising treatment**

- Minimise steroid use
- Sequence therapy appropriately
- Optimise target platelet count
- Optimise timing of therapy
- Use medication for which there is the largest evidence base
- Use indicators other than platelet count, e.g. QoL and fatigue
- Understand the patient’s perspective and anxieties with ITP and its treatment
- Increase patient involvement in the choice of treatment and patient understanding of the impact of ITP on QoL

---

**Moved from “The platelet count is key” to “Platelets plus symptoms (and minimising toxicity) are key”**

AE, adverse event; ITP, immune thrombocytopenia; QoL, quality of life
INFLUENCES ON TREATMENT PATTERNS

• Changes in guidance
  – 1\textsuperscript{st}, 2\textsuperscript{nd}, 3\textsuperscript{rd} line treatment

• Trial data and literature
  – RCT data

• Licensing
  – Changing definitions of persistent and chronic

• Localised and national \textbf{funding arrangements}
  – Links to local and national guidance
CHANGING TREATMENT USE IN THE UK: DATA FROM THE UK (PRIMARY) ITP REGISTRY

- Nationwide registry
- Eligibility criteria
  - > 18 years old
  - Living in UK
  - Platelet count < 100 x 10^9/L
  - No evidence of other cause of thrombocytopenia
- Collects anonymised data
  - Epidemiology
  - Clinical and laboratory features
  - Treatment
- Plus DNA

ITP, immune thrombocytopenia
## DEMOGRAPHICS
### (DATA ANALYSED 1/9/2019)

<table>
<thead>
<tr>
<th>Total number of patients: 3,236</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex, n (%)</strong></td>
</tr>
<tr>
<td>Female</td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>Unknown</td>
</tr>
<tr>
<td><strong>Median (IQR) age at diagnosis, years</strong></td>
</tr>
<tr>
<td>All</td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>Female</td>
</tr>
<tr>
<td><strong>Date of diagnosis, n (%)</strong></td>
</tr>
<tr>
<td>1/12/2008–30/11/2018</td>
</tr>
<tr>
<td>1998–2008</td>
</tr>
<tr>
<td>1988–1998</td>
</tr>
<tr>
<td>&lt; 1988</td>
</tr>
</tbody>
</table>

### Test

<table>
<thead>
<tr>
<th>Test</th>
<th>Data entry (%)</th>
<th>Median (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Full blood count</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haemoglobin (g/L)</td>
<td>100</td>
<td>135 (127–147)</td>
</tr>
<tr>
<td>WBC (x 10⁹/L)</td>
<td>100</td>
<td>7.2 (5.5–9.96)</td>
</tr>
<tr>
<td>Platelets (x 10⁹/L)</td>
<td>100</td>
<td>21 (6–59)</td>
</tr>
<tr>
<td><strong>Coagulation screen</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PT (sec)</td>
<td>100</td>
<td>11.7 (10.7–12.9)</td>
</tr>
<tr>
<td>APTT (sec)</td>
<td>100</td>
<td>28.5 (25.0–21.5)</td>
</tr>
</tbody>
</table>

APTT, activated partial thromboplastin time; IQR, interquartile range; PT, prothrombin time; WBC, white blood cells
# EMERGENCY AND RESCUE THERAPIES

## UK ITP REGISTRY (n = 3,236)

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Participants who received therapy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>prednisolone</td>
<td>70</td>
</tr>
<tr>
<td>dexamethasone</td>
<td>9.4</td>
</tr>
<tr>
<td>methylprednisolone</td>
<td>2.4</td>
</tr>
<tr>
<td>IVIg</td>
<td>42.4</td>
</tr>
</tbody>
</table>

## SPANISH REGISTRY STUDY¹ (n = 433)

Patterns of corticosteroid use as first-line treatment for primary ITP

<table>
<thead>
<tr>
<th></th>
<th>Primary ITP patients, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Corticosteroid(s) as 1st-line treatment</strong></td>
<td>324 (74.8)</td>
</tr>
<tr>
<td>Corticosteroid monotherapy</td>
<td>176 (40.6)</td>
</tr>
<tr>
<td>Corticosteroid + IVIg (± other therapies)</td>
<td>142 (32.8)</td>
</tr>
<tr>
<td>Corticosteroid + other therapies (except IVIg)</td>
<td>6 (1.4)</td>
</tr>
</tbody>
</table>

**Type of corticosteroid**

<table>
<thead>
<tr>
<th>Corticosteroid</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>prednisone</td>
<td>282 (65.1)</td>
</tr>
<tr>
<td>methylprednisolone</td>
<td>52 (12.0)</td>
</tr>
<tr>
<td>dexamethasone</td>
<td>27 (6.2)</td>
</tr>
<tr>
<td>deflazacort</td>
<td>5 (1.1)</td>
</tr>
<tr>
<td>prednisolone</td>
<td>2 (0.5)</td>
</tr>
</tbody>
</table>

ITP, immune thrombocytopenia; IVIg, intravenous immunoglobulin

SECOND-LINE THERAPIES

TPO-RA, thrombopoietin receptor agonist
THIRD-LINE THERAPIES

TPO-RA, thrombopoietin receptor agonist
### OTHER INTERNATIONAL DATA

<table>
<thead>
<tr>
<th></th>
<th>USA(^1) (2011–2016)</th>
<th>CARMEN(^2)</th>
<th>SPANISH(^3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, n</td>
<td>447</td>
<td>90 (primary ITP)</td>
<td>433 (primary ITP)</td>
</tr>
<tr>
<td>Steroids</td>
<td>76% by 1 year from diagnosis</td>
<td>60% (during week of diagnosis)</td>
<td>74.8%</td>
</tr>
<tr>
<td>IVIg</td>
<td>–</td>
<td>43% (during week of diagnosis)</td>
<td>5.8%</td>
</tr>
<tr>
<td>Other treatments (by 1 year)</td>
<td>rituximab 16%</td>
<td>rituximab 11 (12%)</td>
<td>Splenectomy 3.5%</td>
</tr>
<tr>
<td></td>
<td>TPO-RA (both) 14%</td>
<td>TPO-RA 15 (17%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Splenectomy &lt; 4%</td>
<td>Splenectomy 1 (1%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>danazol 7 (8%)</td>
<td></td>
</tr>
</tbody>
</table>

ITP, immune thrombocytopenia; IVIg, intravenous immunoglobulin; TPO-RA, thrombopoietin receptor agonist

WHAT IS KNOWN ABOUT LONG-TERM REMISSION WITH TPO-RA IN CHRONIC ITP?

Vickie McDonald

ITP, immune thrombocytopenia; TPO-RA, thrombopoietin receptor agonist
<table>
<thead>
<tr>
<th></th>
<th>romiplostim</th>
<th>eltrombopag</th>
<th>avatrombopag</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type of molecule</strong></td>
<td>Peptide</td>
<td>Small molecule</td>
<td>Small molecule</td>
</tr>
<tr>
<td><strong>TPO receptor site of action</strong></td>
<td>Extracellular</td>
<td>Transmembrane</td>
<td>Transmembrane</td>
</tr>
<tr>
<td><strong>Potency</strong></td>
<td>8-10 times increased platelet count at maximum dose compared to eltrombopag</td>
<td>-</td>
<td>3-5 times increased platelet count at maximum dose compared to eltrombopag</td>
</tr>
<tr>
<td><strong>Route</strong></td>
<td>Subcutaneously once weekly</td>
<td>Oral, daily</td>
<td>Oral, daily</td>
</tr>
<tr>
<td><strong>Administration considerations</strong></td>
<td>Can patient self-administer injections</td>
<td>Timing in relation to food containing calcium</td>
<td>None</td>
</tr>
<tr>
<td><strong>Safety and tolerability</strong></td>
<td>Well tolerated, low AEs Reticulin and VTE comparable Antibody development</td>
<td>Well tolerated, low AEs Reticulin and VTE comparable Transaminitis</td>
<td>Well tolerated, low AEs VTE comparable Reticulin has not been studied</td>
</tr>
<tr>
<td><strong>Current indications</strong></td>
<td>Chronic ITP (adults and children)</td>
<td>Chronic ITP (adults and children) Hepatitis C-associated thrombocytopenia Severe aplastic anaemia</td>
<td>Periprocedural thrombocytopenia in patients with chronic liver disease Chronic ITP (USA), awaiting regulatory approval in EU</td>
</tr>
</tbody>
</table>

AE, adverse event; ITP, immune thrombocytopenia; TPO, thrombopoietin; VTE, venous thromboembolism
TPO-RAs CAN INDUCE A LONG-LASTING IMMUNOLOGICAL RESPONSE

Increased or improved T-regulatory cell activity

Increased B-regulatory cell activity

Increased TGF-beta (mediates the increased T- and B-regulatory cell activity)

Change in Fc receptors: reversal of Fc receptor balance towards FcRIIb (inhibitory)

Reduces antiplatelet antibody levels in mice with ITP

FcRIIb, Fc receptor IIb; ITP, immune thrombocytopenia; TGF, transforming growth factor; TPO-RA, thrombopoietin receptor agonist

TREATMENT FREE “REMISSION” IN ITP: TERMINOLOGY

• Treatment-free remission vs thrombocytopenia-free remission
  – Significance of terminology
  – Complete response (CR): Platelets ≥ 100 x 10⁹/L
  – (Partial) response: Platelets ≥ 30 x 10⁹/L and two-fold increase from baseline

• Treatment-free remission
  – No longer requiring active therapy, considered low risk for bleeding

• What threshold?
  – Platelets > 50 x 10⁹/L
  – Platelets > 30 x 10⁹/L

• For how long?

• Mazzucconi et al.¹
  – “Durable response”: response or CR lasting ≥ 4 weeks with a stable dose of TPO-RA
  – “Sustained response”: platelet count ≥ 30 x 10⁹/L after > 4 weeks since TPO-RA discontinuation, in the absence of concomitant treatments

ITP, immune thrombocytopenia; TPO-RA, thrombopoietin receptor agonist

# SUSTAINED RESPONSES TO TPO-RA OFF TREATMENT\(^1\)

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients, n</th>
<th>Patients who discontinued TPO-RA, n (% of all patients)</th>
<th>Patients with off-treatment responses, n (% of all patients)</th>
<th>Median follow-up, months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leven et al.</td>
<td>15</td>
<td>5 (33)</td>
<td>5 (33)</td>
<td>6+</td>
</tr>
<tr>
<td>Mahevas et al.</td>
<td>54</td>
<td>20 (37)</td>
<td>8 (15)</td>
<td>13.5</td>
</tr>
<tr>
<td>Cervinek et al.</td>
<td>46</td>
<td>11 (24)</td>
<td>11 (24)</td>
<td>33</td>
</tr>
<tr>
<td>Gonzalez-Lopez et al.</td>
<td>12</td>
<td>12 (100)</td>
<td>12 (100)</td>
<td>7</td>
</tr>
<tr>
<td>Newland et al.</td>
<td>4</td>
<td>3 (75)</td>
<td>3 (75)</td>
<td>29.5</td>
</tr>
<tr>
<td>Marshall et al.</td>
<td>43</td>
<td>12 (28)</td>
<td>12 (28)</td>
<td>20</td>
</tr>
<tr>
<td>Bussel et al.</td>
<td>302</td>
<td>10 (3)</td>
<td>9 (3)</td>
<td>6+</td>
</tr>
<tr>
<td>Carpenedo et al.</td>
<td>27</td>
<td>13 (48)</td>
<td>13 (48)</td>
<td>26</td>
</tr>
<tr>
<td>Mazzucconi et al.(^2)</td>
<td>39</td>
<td>7 (18)</td>
<td>7 (18)</td>
<td>19.4</td>
</tr>
</tbody>
</table>

TPO-RA, thrombopoietin receptor agonist

POSSIBLE CRITERIA TO BE CONSIDERED AS PARAMETERS OF TPO-RA TAPERING AND DISCONTINUATION

<table>
<thead>
<tr>
<th>Patients to consider for tapering</th>
<th>Patients to perhaps not consider for tapering</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with a CR and treated with lower doses of a TPO-RA for ≥ 6 months *</td>
<td>Patients requiring high-dose TPO-RA and platelets &lt; 50 x 10^9/L</td>
</tr>
<tr>
<td>*? CR or lower platelet count acceptable</td>
<td>ITP that was previously hard to manage</td>
</tr>
<tr>
<td>ITP duration: not predictive but better if shorter</td>
<td>TPO-RA &lt; 6/12 months</td>
</tr>
<tr>
<td>Age of patient: not predictive</td>
<td>High risk of bleeding if treatment stopped</td>
</tr>
<tr>
<td>Number of lines of previous treatment: not predictive, but better if low</td>
<td>On concurrent antiplatelets or anticoagulants required to support higher platelet count</td>
</tr>
<tr>
<td></td>
<td>Significant comorbidities, risk of recurrent infection</td>
</tr>
</tbody>
</table>

CR, complete response; ITP, immune thrombocytopenia; TPO-RA, thrombopoietin receptor agonist
HOW TO TAPER:
NO INTERNATIONAL CONSENSUS

EXPERT OPINION

DOSE REDUCTION: HOW QUICKLY?

romiplostim (considering a dose of $x \mu g/kg$ every week before tapering)

- Go to $x - 1 \mu g/kg$ every week
- Go to $x - 2 \mu g/kg$ every week
- Extend the same dose by 1 day
- At fortnightly intervals drop to 75% of $x$, then 50%, then 25%, then 10%, then stop

eltrombopag (considering a dose of 50 mg every day before tapering)

- 37.5 mg daily
- 25 mg daily
- 25 mg alternating with 50 mg
- 50 mg 6 days per week
- 50 mg 5 days per week

Period of tapering and discontinuation (week 25–week 32)

Period of observation (week 33–week 52)

EXPERT OPINION

HOW DO WE MONITOR TAPERING AND DEFINE FAILURE?

MONITOR: HOW CLOSELY?
Time to platelet-count monitoring after initiating TPO-RA dose reduction

- 3 days
- 7 days
- 14 days
- 21 days
- 28 days

TAPER FAILURE?
If you are tapering off TPO-RA, below which platelet count would you reinstitute treatment or stop tapering or add another treatment?

- 75 x 10^9/L
- 50 x 10^9/L
- 30 x 10^9/L
- 20 x 10^9/L

Which criteria should we use?
- Platelet count: 50 vs 30 vs 20 x 10^9/L
- Bleeding
- QoL

Trial data needed: TAPER^1

QoL, quality of life; TPO-RA, thrombopoietin receptor agonist
ACKNOWLEDGEMENTS

UK ITP registry team
H Miah
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D Provan
A Newland

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D A Zaidi

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Dr H Ahmad  Queen’s Hospital Burton
Dr D Allotey  Royal Derby Hospital / University Hospitals of Derby and Burton NHS Foundation Trust
Dr D Allsup  Castle Hill Hospital
Dr M Almusaww  Bedford Hospital
Dr M Alobaidi  West Middlesex University Hospital
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Dr B Austen  Yewil District Hospital
Dr S Austin  St George’s Hospital
Dr C Bagot  Glasgow Royal Infirmary
Dr W Bashir  Glamorgan Hospital. Wales
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Dr C Bradbury  University Hospitals Bristol NHS Foundation Trust
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Dr O Chapman  Worcestershire Royal Hospital
Dr S Chattree  Sunderland Royal Hospital
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Dr J Coppell  Royal Devon & Exeter Hospital
Dr J Crowe  Royal United Hospital Bath NHS Trust
Dr R Dang  The James Cook University Hospital
Dr S Davies  Musgrove Park Hospital
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Dr F Jack  Poole Hospital NHS Foundation Trust
Dr H Jackson  Aneurin Bevan University Health Board, Nevill Hall, Royal Gwent
Dr S Johns  Royal Cornwall Hospital
Dr M Karanth  West Suffolk Hospital
Dr M Kliner  Northumbria Healthcare NHS Foundation Trust
Dr M Kmonicek  North Bristol NHS Trust / South Mead Hospital
Dr O Kreze  Newham University Hospital
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Dr V McDonald  The Royal London Hospital
Dr M Mohan  Colchester General Hospital
Dr T Moorby  Sherwood Forest Hospitals NHS Foundation Trust, King’s Mill Hospital
Dr L Munro  Scarborough Hospital, York Teaching Hospital NHS Foundation Trust
Prof M Murphy  Oxford University Hospitals NHS Foundation Trust / The Churchill Hospital
Dr V Murphy  Heartlands Hospital
Dr M Mushibar  University Hospitals Coventry and Warwickshire NHS Trust
Dr J Neilson  Russells Hall Hospital / The Dudley Group NHS Foundation Trust
Dr E Nga  Airedale NHS Foundation Trust
Dr T Nokes  Plymouth Hospitals NHS Trust, Derriford Hospital
Dr R Oakes  North Cumbria University Hospitals NHS Trust
Dr M Offer  Frimley NHS Trust - previously Heathwood & Wexhampark Hospitals NHS Foundation Trust
Dr R Raymond  Cardiff and Vale, University Hospital of Wales
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Dr N Sargent  Basingstoke & North Hampshire Hospital; Royal Hampshire County Hospital, Winchester
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Dr M Srivakumar  North West Anglia Foundation Trust, Peterborough City Hospital
Dr J Tam  Chesterfield Royal Hospital NHS Foundation Trust
Dr J Thachil  Manchester Royal Infirmary / Manchester University NHS Foundation Trust
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ITP, immune thrombocytopenia
WHAT IS THE LONG-TERM SAFETY PROFILE OF TPO-RA\textsubscript{s}? 

David J. Kuter
POTENTIAL ADVERSE CONSEQUENCE OF THROMBOPOIETIC GROWTH FACTORS

- Thrombocytosis
- **Thrombosis**
- Stimulation of tumour growth
- Stimulation of leukaemia cell growth
- Interactions with other cytokines

- **Autoantibody formation**
- Stem cell depletion
- Reduction of threshold for platelet activation
- **Rebound worsening of thrombocytopenia**
- Increased bone-marrow reticulin
**POOLED ANALYSIS: THROMBOTIC EVENTS IN ALL ROMIPLOSTIM STUDIES**

<table>
<thead>
<tr>
<th></th>
<th>Romiplostim</th>
<th>Placebo or SOC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>n</strong></td>
<td>n = 994</td>
<td>n = 138</td>
</tr>
<tr>
<td><strong>1,520 pt-yr</strong></td>
<td>1,520 pt-yr</td>
<td>110 pt-yr</td>
</tr>
<tr>
<td><strong>Thrombotic or thromboembolic events</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>83 (8.4%)</td>
<td>6 (4.3%)</td>
</tr>
<tr>
<td></td>
<td><strong>5.5/100 pt-yr</strong></td>
<td><strong>5.5/100 pt-yr</strong></td>
</tr>
<tr>
<td></td>
<td>CI 4.4–6.8</td>
<td>CI 2.0–11.9</td>
</tr>
<tr>
<td><strong>Serious thrombotic or thromboembolic events</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>61 (6.5%)</td>
<td>2 (1.4%)</td>
</tr>
<tr>
<td></td>
<td><strong>4.0/100 pt-yr</strong></td>
<td><strong>1.8/100 pt-yr</strong></td>
</tr>
<tr>
<td></td>
<td>CI 3.1–5.2</td>
<td>CI 0.2–6.6</td>
</tr>
</tbody>
</table>

No relation with platelet count

CI, confidence interval; pt-yr, patient-years; SOC, standard of care
NO RELATION BETWEEN PLATELET COUNT AND THROMBOSIS EVENTS

ITP, immune thrombocytopenia; pt-yr, patient-years
ANTIBODIES TO TPO-RA (ROMIPLOSTIM) ARE RARE

- No TPO-neutralising antibodies
- No effect on platelet count

TPO, thrombopoietin; TPO-RA, thrombopoietin receptor agonist
DANGER OF WITHHOLDING A DOSE

### Platelet count
- **Mean (SD)**: 239 (328)
- **Median (range)**: 53 (5–1,257)

### Dose
- **Mean (SD)**: 4 (2) μg/kg
- **Median (range)**: 4 (0–6) μg/kg

SD, standard deviation
BONE MARROW FIBROSIS: PROSPECTIVE TRIALS

• NCT00907478: a prospective study evaluating changes in bone marrow morphology in adult subjects receiving romiplostim for the treatment of thrombocytopenia associated with ITP\(^1,2\)
  – Bone marrow studies at baseline and after 1, 2, and 3 years of treatment
  – Primary endpoint: rate of collagen fibrosis
  – Multiple secondary endpoints: reticulin

• NCT01098487: a longitudinal 2-year bone marrow study of eltrombopag in previously treated adults with chronic ITP\(^3,4\)
  – Bone marrow studies at baseline and after 1 and 2 years of treatment

ITP, immune thrombocytopenia

INCIDENCE OF BONE MARROW FIBROSIS IN ITP PATIENTS TREATED WITH ROMIPLOSTIM

<table>
<thead>
<tr>
<th></th>
<th>After 1 year (n = 50)</th>
<th>After 2 years (n = 50)</th>
<th>After 3 years (n = 69)</th>
<th>All groups (n = 169)</th>
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</thead>
<tbody>
<tr>
<td>Evaluable for collagen (trichrome stain), n</td>
<td>42</td>
<td>38</td>
<td>52</td>
<td>132</td>
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<tr>
<td>Positive for collagen, n (%)</td>
<td>1 (2.4)</td>
<td>0</td>
<td>1 (1.9)</td>
<td>2 (1.5)</td>
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<tr>
<td>Evaluable for reticulin (silver stain), n</td>
<td>41</td>
<td>38</td>
<td>52</td>
<td>131</td>
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<tr>
<td>Reticulin increase by ≥ 2 grades, n (%)</td>
<td>2 (4.9)</td>
<td>1 (2.6)</td>
<td>4 (7.7)</td>
<td>7 (5.3)</td>
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</tbody>
</table>

ITP, immune thrombocytopenia
INCIDENCE OF BONE MARROW FIBROSIS IN ITP PATIENTS TREATED WITH ELTROMBOPAG

ITP, immune thrombocytopenia; MF, marrow fibrosis (European Consensus scale)
CURRENT CHALLENGES AND NOVEL TREATMENT OPTIONS IN ITP

Jerzy Windyga
David J. Kuter
Vickie McDonald
CASE: MR RUSSO
PART 1

PATIENT FROM A HIGH-RISK CORONAVIRUS AREA PRESENTS WITH ITP

53-year-old man presents with bleeding gums and generalised petechiae

History of episodes of bleeding gums and easy bruising, type 2 diabetes, and rheumatoid arthritis

Platelet count 16 x 10^9/L
Other haematological and biochemical parameters and liver function tests normal

Recently visited family in northern Italy

COVID-19, coronavirus disease 2019; ITP, immune thrombocytopenia
CASE: MR RUSSO
PART 1

PATIENT FROM A HIGH-RISK CORONAVIRUS AREA PRESENTS WITH ITP

1. Is hospitalisation required?
2. What should be the first-line therapy?
3. Has COVID-19 changed the role of steroids in the treatment of ITP?
4. What can be done to minimize the number of hospital visits?

How would you treat this patient in the COVID-19 era?
PATIENT DEVELOPS REFRACTORY ITP

3 years later, Mr Russo still regularly has bleeding gums, petechiae, and blood in stool, despite treatment with a TPO-RA.

What novel treatment options are in the pipeline to treat a patient with refractory, chronic ITP?
WHAT NOVEL DRUGS ARE IN THE PIPELINE TO TREAT THIS PATIENT?

David J. Kuter
NOVEL THERAPIES FOR ITP

- **FcRn pathway inhibitors**
  - Increase clearance of antiplatelet antibody

- **Anti-CD38 molecules**
  - Inhibit plasma cells

- **Anti-CD40 ligand antibodies**
  - Reduce production of antiplatelet antibody

- **Immunoproteasome inhibitor**
  - Reduces antibody

- **Sialylated IgG**
  - Blocks macrophage FcR

- **Stradomers**
  - Recombinant Fc multimers reduce phagocytosis

- **Bruton kinase inhibitors**
  - Ibrutinib
  - Rilzabrutinib (PRN1008)

- **Syk kinase inhibitors**
  - Fostamatinib

- **Complement inhibitor**
  - Antibody against C1s

- **Recombinant TPO**
  - Use in pregnancy

- **Low-level laser light**
  - Prevents megakaryocyte apoptosis

FcR(n), (neonatal) Fc receptor; ITP, immune thrombocytopenia; Syk, spleen tyrosine kinase; TPO, thrombopoietin
Btk, Bruton tyrosine kinase; FcγRIII, Fc gamma receptor III; PI3K, phosphatidylinositol-3 kinase; PLCγ, phospholipase C gamma; Syk, spleen tyrosine kinase

Btk, Bruton tyrosine kinase; FcγRIII, Fc gamma receptor III; FcRn, neonatal Fc receptor; PI3K, phosphatidylinositol-3 kinase; PLCγ, phospholipase C gamma; Syk, spleen tyrosine kinase

Btk, Bruton tyrosine kinase; FcγRIII, Fc gamma receptor III; PI3K, phosphatidylinositol-3 kinase; PLCγ, phospholipase C gamma; Syk, spleen tyrosine kinase

Btk, Bruton tyrosine kinase; ER, endoplasmic reticulum; FcγRIII, Fc gamma receptor III; IP3, inositol trisphosphate; ITAM, immunoreceptor tyrosine-kinase-based activation motifs; PIP3, phosphatidylinositol (3,4,5)-trisphosphate; PKC, protein kinase C; PI3K, phosphatidylinositol-3 kinase; PLCγ, phospholipase C gamma; Syk, spleen tyrosine kinase

Btk, Bruton tyrosine kinase; FcγRIII, Fc gamma receptor III; PI3K, phosphatidylinositol-3 kinase; PLCγ, phospholipase C gamma;
Syk, spleen tyrosine kinase

Btk, Bruton tyrosine kinase; FcγRIII, Fc gamma receptor III; PI3K, phosphatidylinositol-3 kinase; PLCγ, phospholipase C gamma; Syk, spleen tyrosine kinase

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Btk, Bruton tyrosine kinase; FcγRIII, Fc gamma receptor III; PI3K, phosphatidylinositol-3 kinase; PLCγ, phospholipase C gamma; Syk, spleen tyrosine kinase

1. Antiplatelet antibody attacks megakaryocyte
2. Lymphocyte attacks megakaryocyte
3. Megakaryocyte undergoes apoptosis

- TPO Receptor

Antiplatelet antibody
Antiplatelet lymphocyte

Recombinant TPO
Low-level laser light

TPO, thrombopoietin
SUMMARY
There is a range of medical options for the subsequent treatment of adults with primary ITP, including rituximab and TPO-RAs.

TPO-RAs have shown compelling evidence of platelet response and reduced bleeding; recent data indicate TPO-RAs are as effective in early ITP as chronic ITP.

TPO-RAs can induce a long-lasting immunological response, however no consensus currently exists on when and how to taper.

Key AEs associated with TPO-RAs include thrombosis, autoantibody formation, rebound worsening of thrombocytopenia and increased bone-marrow reticulin.

Unmet needs remain in this disease area, requiring further research and consensus; novel drugs are expected in the years to come.

AE, adverse event; ITP, immune thrombocytopenia; TPO-RA, thrombopoietin receptor agonist
APPENDIX
# ISTH 2020 ABSTRACTS ON THE TREATMENT OF CHRONIC ITP IN ADULTS

<table>
<thead>
<tr>
<th>Abstract number</th>
<th>First author</th>
<th>Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>PB1316</td>
<td>J. Agnelli Giacchello</td>
<td>Megakaryocytic Hyperplasia in Bone Marrow Biopsy as a Novel Predictor of Response in Patients with Immune Thrombocytopenia</td>
</tr>
<tr>
<td>PB1318</td>
<td>D. Kuter</td>
<td>Phase I/II, Open-Label, Ongoing Study of PRN1008 (Rilzabrutinib), an Oral Bruton Tyrosine Kinase Inhibitor, in Patients with Heavily Pretreated Immune Thrombocytopenia (ITP)</td>
</tr>
<tr>
<td>PB1335</td>
<td>I. Altomare</td>
<td>Achieving Clinically Relevant Platelet Count Response Thresholds with Avatrombopag (AVA) in Immune Thrombocytopenia (ITP)</td>
</tr>
<tr>
<td>PB1343</td>
<td>J. Yamanouchi</td>
<td>Sustained Remission after Withdrawal of Thrombopoietin Receptor-Agonists in Immune Thrombocytopenia</td>
</tr>
<tr>
<td>PB1344</td>
<td>P. Zhao</td>
<td>Risk Stratification for Intracranial Hemorrhage in Adults with Immune Thrombocytopenia: A Retrospective Multicenter Study</td>
</tr>
<tr>
<td>PB1345</td>
<td>J. Gebhart</td>
<td>Factors Influencing Bleeding Severity in Adult Patients with Primary Immune Thrombocytopenia</td>
</tr>
<tr>
<td>PB1346</td>
<td>M. Stimpson</td>
<td>CD4+ T Cell Expression of IL-10 Compared to IL-17 is Lower in Patients with Immune Thrombocytopenia (ITP) Who Do Not Respond Clinically to High Dose Corticosteroid</td>
</tr>
<tr>
<td>PB1349</td>
<td>H. Maitland</td>
<td>Response to Avatrombopag (AVA) in Chronic Immune Thrombocytopenia: Alternative Efficacy Measures</td>
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<tr>
<td>PB1350</td>
<td>N. Gabrail</td>
<td>Pharmacokinetic/Pharmacodynamic (PK/PD) Modeling Providing Guidance for Selecting Avatrombopag (AVA) Dose when Switching from Eltrombopag in Chronic Immune Thrombocytopenia (ITP)</td>
</tr>
<tr>
<td>PB1357</td>
<td>M. Marcosano</td>
<td>Long Term Complications after Splenectomy in Chronic pITP Patients: A Retrospective Case Control Study</td>
</tr>
<tr>
<td>PB1358</td>
<td>W. Ghanima</td>
<td>Fostamatinib as Second-Line Therapy for ITP and in Earlier Stage ITP Patients</td>
</tr>
<tr>
<td>PB1359</td>
<td>M.G. Mazzucconi</td>
<td>Randomized Study for the Treatment of Primary Immune Thrombocytopenic Purpura (pITP) in Newly Diagnosed Untreated Adult Patients. Comparison of Standard Dose Prednisone versus High-dose Dexamethasone. Preliminary Results. GIMEMA Protocol ITP0207</td>
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<td>PB1363</td>
<td>M.G. Mazzucconi</td>
<td>Response Rate and Response Duration after Discontinuation of Treatment with Thrombopoietin Receptor Agonists (TPO-RAS) in Patients Affected by Primary Immune Thrombocytopenia (pITP): Retrospective Study. Preliminary Results. GiMema Protocol ITP0714</td>
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<td>PB1378</td>
<td>M. Recht</td>
<td>Corticosteroid Reduction or Discontinuation after Initiation of Avatrombopag Treatment in Patients with Chronic Immune Thrombocytopenia (ITP)</td>
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ISTH, International Society on Thrombosis and Haemostasis; ITP, immune thrombocytopenia