Clinical Indications for Thrombopoietin and Thrombopoietin-Receptor Agonists

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Summary
Thrombocytopenia is a common hematologic disorder. Stimulation of thrombopoiesis may reduce the risk for thrombocytopenia-induced bleeding, prevent severe thrombocytopenia, and reduce the need for platelet transfusion. The key cytokine is thrombopoietin (TPO). It regulates proliferation and maturation of megakaryocytes as well as platelet production. TPO is synthesized in the liver. Development of TPO from the laboratory into a therapeutic tool has turned out to be an unexpected challenge. Clinical trials on first-generation thrombopoietic growth factors were stopped in 2001. At present, second-generation thrombopoiesis-stimulating agents have only been approved as orphan drugs for third-line therapy of patients with chronic immune thrombocytopenia. Larger groups in need are patients with myelodysplastic syndrome, chemotherapy-induced thrombocytopenia, other forms of hereditary and acquired bone marrow failure, hepatitis C infections, or liver cirrhosis.

Introduction
Thrombocytopenia is a common hematological disorder [1]. Grading of severity is based on the number of platelets in the peripheral blood. Only patients with platelets below 30,000/μl have an increased risk of spontaneous bleeding. Severe bleeding may occur with platelets <10,000/μl, which is also dependent on other risk factors that affect platelet function. Patients with thrombocytopenia due to deficient platelet production are at higher risk of bleeding than patients with the same low platelet counts due to increased destruction.

The most efficient therapy in thrombocytopenia-induced bleeding is transfusion of platelet concentrates, obtained either by apheresis or prepared from buffy coats of whole-blood donations [2]. In Germany, more than 500,000 platelet concentrates are prepared per year [3]. The need in the USA is similar with about 1,500,000 units per year. A substantial proportion of platelet concentrates is given prophylactically in patients with severe thrombocytopenia.

Since platelet concentrates are derived from the blood of healthy donors, they are a valuable resource. Risks of repeated transfusions include alloimmunization and the transmission of hitherto unidentified infectious agents.

Thrombocytopenia is a frequent problem in the management of patients with chemotherapy-induced thrombocytopenia as well as in patients with myelodysplastic syndrome (MDS), chronic liver disease, and immune thrombocytopenia (ITP). The approval of the second-generation thrombopoietic growth factors romiplostim and eltrombopag for the treatment of patients with ITP has raised hopes for broad application. We present and discuss data for the different clinical indications.

Megakaryopoiesis and Thrombopoiesis

Megakaryopoiesis and platelet production are complex processes. Both are regulated via positive and negative signals [4, 5]. Megakaryocytes are derived from pluripotent hematopoietic stem cells. In the course of their differentiation, megakaryocytic progenitors lose their proliferative capacity and develop into mature, polyploid megakaryocytes. It has been
estimated that megakaryocytes maintain a steady production of 10^11 platelets per day. Production can be increased ‘on demand’ by a factor of 10 or more.

Multiple growth factors are involved in the external regulation of megakaryopoiesis. IL-3, IL-6, IL-11, and stem cell factor have megakaryocyte colony-stimulating activity, but the key cytokine is thrombopoietin (TPO). Synonyms are megakaryocyte-derived growth factor (MGDF) or c-mpl ligand.

TPO was a late starter in the class of hematopoiesis-regulating cytokines [6]. It was first identified via its cellular receptor, the homologue of the viral oncogene v-mpl. C-mpl has a characteristic receptor structure with a large extracellular domain, a transmembrane region and an intracellular domain. Cloning of the receptor ligand lead to the almost simultaneous description of TPO by five independent groups in 1994 [7–13]. Interaction of TPO with its receptor leads to association of the intracellular domain with the tyrosine kinase Jak2. Signaling pathways include JAK-STAT, MAPK-ERK1/2 and PI3K-AKT [14]. TPO is a class I hematopoietic cytokine. It consists of 355 amino acids; the first 155 are homologous to erythropoietin. TPO regulates proliferation and maturation of megakaryocytes as well as platelet production. In addition, it also increases the number erythroid and myeloid progenitors, mostly likely due a synergy with other hematopoietic growth factors. TPO is synthesized in the liver.

Elimination of either c-mpl or TPO in mice leads to decreased number of megakaryocytes, reduced polyploidy and profound thrombocytopenia. This disease pattern is strikingly similar to the previously described human syndrome of congenital amegakaryocytic thrombocytopenia (CAMT) [15]. It is now clear, that the majority of CAMT is induced by mutations in the c-mpl gene [16, 17]. CAMT type I and II are distinguished based on severity of thrombocytopenia and type of mutation [18].

While hereditary TPO defects have not yet been described as origin of thrombocytopenia, inherited TPO mutations are responsible for thrombocythemia 1, one of the genetically heterogeneous disorders of hereditary thrombocythemia [19, 20].

Development of Thrombopoietic Agents in Humans

Following the identification of TPO, two recombinant molecules were rapidly developed into drugs for use in medicine. Full-length recombinant, heavily glycosylated human TPO (rhTPO) was synthesized in Chinese hamster ovary cells. A single dose resulted in an increase of platelets by day 4–5 with a median peak on days 10–14 [21].

An alternative approach used a truncated, non-glycosylated form of TPO produced in Escherichia coli. The substance was called megakaryocyte growth and differentiation factor (MGDF). It consisted of the 163 amino-terminal amino acids, coupled to polyethylene glycol for stabilization. In healthy platelet donors, a single subcutaneous injection resulted in a significant increase of platelets by day 5–6 with a maximum by day 12 [22].

A number of clinical trials in different indications were initiated including chemotherapy-induced thrombocytopenia [23, 24], stem cell mobilization for autologous transplantation, and platelet mobilization in healthy donors [25]. In one of the pegylated recombinant human MGDF (PEG-rHuMGDF) studies in healthy volunteers, 13 persons developed antibodies which cross-reacted with endogenous TPO [26]. This adverse event resulted in prolonged thrombocytopenia and the discontinuation of all clinical studies with rhTPO and PEG-rHuMGDF. Neither of the substances reached the stage of approval as new drug.

These now called first-generation thrombopoietic growth factors were followed by an intensive period of research for agents, which mimic TPO without any sequence homology to endogenous TPO and the risk of antibody formation [27, 28]. Candidates included peptides, non-peptides, and agonistic antibodies. The second-generation thrombopoietic growth factors are also called thrombopoietin receptor agonists (TPO-RA or TRA). Two of them, eltrombopag and romiplostim, have already been approved by the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA). Others such as AKR-501 are in clinical trials.

Romiplostim (Nplate®, Amgen GmbH, Munich, Germany) is a so-called peptibody. It consists of four peptides coupled by glycine bridges to a heavy-chain fragment of immunoglobulin G [29]. Romiplostim binds specifically to c-mpl and induces dimerization of the receptor. After single injection, it induces an increase of platelets with a maximum around day 15. Adverse effects include headaches, nausea, arthralgia, and thromboembolic events. Romiplostim is administered subcutaneously once weekly.

The second substance is eltrombopag (Revolade®, Promacta®, GlaxoSmithKline GmbH, Munich, Germany) [30]. It is a small non-peptide molecule that binds to the transmembrane part of the TPO receptor. It is structurally distinct from endogenous TPO. Peak response occurs on days 15–16. Eltrombopag is well tolerated. Side effects include headaches, nausea and vomiting, thromboembolic events, and elevations in alanine transaminase and bilirubin. Eltrombopag is administered orally.

Early reports in romiplostim-treated patients had raised concerns about increased reticulin deposition in the bone marrow. Follow-up studies showed alterations in a low number of patients. These alterations do not seem to progress into bone marrow fibrosis and were reversible on stop of the drugs [28].

Immune Thrombocytopenia

ITP is an acquired disorder [31, 32]. In Germany, it was also called Morbus Werlhof, honoring an 18th century publication of thrombocytopenic symptoms by a physician from
Both drugs induce a high response rate. The impact on serious bleeding or mortality can only be estimated. The trials were not powered to detect a significant difference in these endpoints [42]. This is also due to low number of hemorrhages in the control arms. At present, no head-to-head comparison between eltrombopag and romiplostim has been published. An increasing number of observations confirm that there is no cross-resistance between the two drugs [43, 44]. In patients who fail to respond to eltrombopag or romiplostim, switch to the other drug may be beneficial.

Unfortunately, most patients with chronic ITP relapse on discontinuation of either drug and have to set in for lifelong therapy. However, a small proportion does not experience relapse. Analysis of platelet kinetics may identify this subset of patients [45].

The pivotal trials led to the approval of romiplostim by the European Medicines Agency (EMA) in 2009 and of eltrombopag in 2010. Both drugs have an orphan drug status. Since high platelet counts are associated with a higher risk for thrombembolic complications, it is recommended to maintain platelets $\leq 50,000/\mu l$. There is no clinical need to achieve levels above 100,000/\mu l. Thus far, no significant and unexpected long-term toxicity has been observed either with eltrombopag or romiplostim in patients with chronic ITP.

Debate about the indication for the use of TRA in ITP is ongoing. First-line treatment in patients with symptomatic disease is immunosuppression with high-dose steroids [31, 32, 33, 34].

### Table 1. Randomized clinical trials with TRA in ITP

| Author / study | Patients | Control | New therapy | N$^a$ | Response rate$^b$ (HR, OR) | Durable response$^c$
<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>Bussel, 2007</td>
<td>TRA 100773A [37]</td>
<td>chronic ITP, 2nd or 3rd line</td>
<td>placebo</td>
<td>Elt 50$^d$</td>
<td>59</td>
<td>11 vs. 70$^e$ p &lt; 0.001</td>
</tr>
<tr>
<td>Bussel, 2007</td>
<td>TRA 100773A [37]</td>
<td>chronic ITP, 2nd or 3rd line</td>
<td>placebo</td>
<td>Elt 75</td>
<td>57</td>
<td>11 vs. 81 p &lt; 0.001</td>
</tr>
<tr>
<td>Bussel, 2009</td>
<td>TRA 100773B [38]</td>
<td>chronic ITP, 2nd or 3rd line</td>
<td>placebo</td>
<td>Elt 50</td>
<td>114</td>
<td>16 vs. 59 p &lt; 0.0001</td>
</tr>
<tr>
<td>Cheng, 2011 RAISE [39]</td>
<td>chronic ITP, 2nd or 3rd line</td>
<td>placebo</td>
<td>Elt 50</td>
<td>197</td>
<td>28 vs. 79 OR 8.20$^f$ p &lt; 0.0001</td>
<td>0 vs. 60 p &lt; 0.0001</td>
</tr>
<tr>
<td>Kuter, 2008 [40]</td>
<td>chronic ITP after splenectomy</td>
<td>placebo</td>
<td>Rom</td>
<td>63</td>
<td>0 vs. 79 p &lt; 0.0001</td>
<td>0 vs. 38 p = 0.0013</td>
</tr>
<tr>
<td>Kuter, 2008 [40]</td>
<td>chronic ITP no splenectomy</td>
<td>placebo</td>
<td>Rom</td>
<td>62</td>
<td>14 vs. 88 p &lt; 0.0001</td>
<td>5 vs. 56 p &lt; 0.0001</td>
</tr>
<tr>
<td>Kuter, 2010 [41]</td>
<td>chronic ITP, no splenectomy</td>
<td>placebo</td>
<td>Rom</td>
<td>234</td>
<td>26 vs. 81 OR 2.3$^i$ p &lt; 0.001</td>
<td>0 vs. 38 p = 0.0013</td>
</tr>
</tbody>
</table>

HR = Hazard ratio; OR = odds ratio; Elt = eltrombopag; Rom = romiplostim.

$^a$Number of patients.

$^b$% of patients with $\geq 50,000/\mu l$ at the prespecified endpoint.

$^c$% of patients with $\geq 50,000/\mu l$ for at least 6 weeks.

$^d$Number indicates the dose in mg.

$^e$Results for controls vs. results for new therapy.

$^f$HR or OR for new therapy.

Lower Saxony. Another synonym was idiopathic thrombocytopenia purpura. ITP is sub-classified into primary and secondary ITP. The origin of primary ITP is unknown. Secondary ITP may be induced by infections, autoimmune diseases, lymphatic neoplasias, solid tumors, drugs, or other causes. While ITP in children is usually self-limited, ITP in adults tends to be a chronic disease. Incidence is 2–4 newly diagnosed patients per 100,000/year in adults and 5–6 per 100,000/year in children.

ITP can also be classified according to the clinical course. This classification distinguishes three stages [33, 34]:

- newly diagnosed or transient (during the first 3 months),
- persistent (3 to 12 months),
- chronic (>12 months).

The immune dysregulation in ITP leads to accelerated destruction of autoantibody-coated platelets in the reticuloendothelial systems and to a suppression of megakaryocyte-derived platelet production in the bone marrow. Physiologically, TPO levels increase with decreasing platelet counts. In ITP patients, TPO levels are lower than expected [35]. In a phase II/I study, 4 patients with refractory ITP received PEG-rHuMGDF [36]. 3 of 4 showed increase of platelet counts, 2 of them with elevations to more than 700,000/\mu l.

This basis and the clinical need prompted clinical studies with second-generation TPO receptor agents. Randomized clinical trials have compared eltrombopag or romiplostim to placebo. Data are summarized in table 1.
The incidence of clinically significant thrombocytopenia-associated events is lower under treatment with romiplostim compared to placebo. There is no clear dose relation. The number of platelet transfusions or of patients who received platelet transfusions is somewhat lower in the romiplostim group, but not consistently. The studies were not powered to detect differences in bleeding episodes or mortality. In the lenalidomide trial, dose reduction was lower in the romiplostim than in the placebo groups [51].

The major concern in MDS is transformation in acute leukemia. This transformation occurs in the natural course of MDS. The rate is higher in the intermediate-2 and high-risk groups. Two patients with acute myeloid leukemia were described in the first phase II study [49], and in case reports thereafter [53]. Only results of large phase III trials can adequately weigh the benefits of thrombopoiesis-stimulating agents versus the potential risks.

**Myelodysplastic Syndrome**

MDS is probably the most challenging hematologic disorder for thrombopoiesis-stimulating agents. The median age of newly diagnosed MDS patients is 75 years [47]. Due to the demographic development, the number of MDS patients is increasing. Progressive thrombocytopenia is a common feature of this neoplastic disorder [48]. Patients with very low platelets counts may receive regular prophylactic platelet transfusions over a prolonged period of months and up to years.

Early phase II trials showed positive effects of romiplostim on platelets counts in patients with MDS [49]. Thus far, results from three small randomized phase III studies have been published [50–52]. They all tested romiplostim in patients with low or intermediate-1 risk patients under treatment with histone deacetylase inhibitors or lenalidomide. Data are summarized in table 2.

<table>
<thead>
<tr>
<th>Author / study</th>
<th>Patients</th>
<th>Control</th>
<th>New therapy</th>
<th>N</th>
<th>CSTE</th>
<th>Platelet transfusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kantarjian, 2010 [50]</td>
<td>MDS, low and intermediate-1 risk, azacitidine</td>
<td>placebo</td>
<td>Rom 500</td>
<td>26</td>
<td>85 vs. 62</td>
<td>79 vs. 105</td>
</tr>
<tr>
<td>Kantarjian, 2010 [50]</td>
<td>MDS, low and intermediate-1 risk, azacitidine</td>
<td>placebo</td>
<td>Rom 750</td>
<td>25</td>
<td>85 vs. 71</td>
<td>79 vs. 34</td>
</tr>
<tr>
<td>Wang, 2012 [51]</td>
<td>MDS, low and intermediate-1 risk, lenalidomide</td>
<td>placebo</td>
<td>Rom 500</td>
<td>26</td>
<td>67 vs. 29</td>
<td>33 vs. 29</td>
</tr>
<tr>
<td>Wang, 2012 [51]</td>
<td>MDS, low and intermediate-1 risk, lenalidomide</td>
<td>placebo</td>
<td>Rom 750</td>
<td>25</td>
<td>67 vs. 62</td>
<td>33 vs. 31</td>
</tr>
<tr>
<td>Greenberg, 2013 [52]</td>
<td>MDS, low and intermediate-1 risk, decitabine</td>
<td>placebo</td>
<td>Rom 750</td>
<td>29</td>
<td>79 vs. 80</td>
<td>57 vs. 47</td>
</tr>
</tbody>
</table>

CSTE = Clinically significant thrombocytopenic event; Elt = eltromboag; Rom = romiplostim.

*a*Number of patients.

*b*Number of transfusions or rate of transfused patients.

*c*Number indicates the dose in mg.

*d*Results for controls vs. results for new therapy.

*e*Number of platelet transfusions.

*f*Rate of patients with platelet transfusions.

Intravenous immunoglobulin, anti-D immunoglobulin, or platelet transfusions are used in emergencies. Recommendation for second-line treatment in corticoid-refractory disease is splenectomy. Splenectomy induces long-term remission, most likely cure, in 50–80% of patients. However, it is a surgical intervention and associated with an increased long-term risk for specific infections. In Europe, TRA are approved for patients with chronic ITP after splenectomy. At this stage, they compete with other forms of immunosuppression such as rituximab. On the individual level, patients’ preferences play an important role in the final decision between splenectomy and drug therapy.

The German guideline recommends TRA only after splenectomy, also with respect to the unknown risks of a lifelong drug therapy. This is in line with the recommendations of the American Society of Hematology [46].

**Chemotherapy-Induced Thrombocytopenia**

Chemotherapy-induced myelosuppression results in various degrees of neutropenia, anemia, and thrombocytopenia. While myeloid growth factors are well established in the prevention of neutropenic complications, and erythropoiesis-stimulating agents may safely be given to some patients with hemoglobin content between 9 and 11 g/dl, no drug is approved for prevention of severe thrombocytopenia and bleeding complications. Platelet transfusions are an effective and rapid treatment for patients with thrombocytopenia-induced bleeding. Prophylactic administration lowers the risk for hem-
or hemorrhages. It has now been established, that platelet counts < 10,000/μl are an adequate trigger for prophylactic platelet transfusions in patients without further risk factors [54]. Very recently, the benefit of platelet transfusions itself has been re-examined in two large randomized clinical trials [55, 56]. In both studies, prophylactic platelet transfusions reduced the risk of bleeding CTCAE grades 2–4. However, this effect was not seen in patients after autologous stem cell transplantation, questioning the current standard of care in this specific therapeutic situation.

The demand for prophylactic or interventional transfusion of platelets in patients with hematological or non-hematological neoplasias contributes considerably to the resource burden in transfusion medicine. When first-generation thrombopoiesis-stimulating growth factors became available, randomized and observational clinical trials were performed in different entities. Studies on patients with sarcoma, lung cancer, and other solid tumors showed that PEG-rHuMGDF or rhTPO may increase the nadir platelet counts, shorten the duration of thrombocytopenia and reduce the need for platelet transfusions [21, 23, 24, 57]. Data analysis also revealed that stimulation of thrombopoiesis is complex. Observations may be summarized as follows:

– The peak of platelets counts occurs on days 10–14; these late effects limit the prophylaxis to drugs with late platelet nadirs, e.g. carboplatin, if thrombopoiesis is stimulated after chemotherapy.
– In one randomized trial, the benefit was significant only in the first two of 6 cycles of a carboplatin-paclitaxel-containing regimen [24].
– In patients with acute myeloid leukemia no significant shortening of the time of critical thrombocytopenia was observed, probably due to the low number of megakaryocytes after induction chemotherapy [58, 59].
– Platelets counts rose as high as 1,000,000/μl.
– The optimal timing of application was not established; application prior to chemotherapy may increase benefit.

An early randomized clinical trial using eltrombopag in patients receiving carboplatin/paclitaxel did not meet the end-point of a significant difference in platelet counts between day 1 of cycle 2 and the nadir of cycle 2 [60]. These data confirm the need for optimization of timing [61]. Currently, eltrombopag or romiplostim are not recommended for the prophylaxis of chemotherapy-induced thrombocytopenia.

### Other Bone Marrow Failure Syndromes

Different forms of hereditary or acquired bone marrow failure syndromes are associated with severe thrombocytopenia [62]. Thrombocytopenia is a major cause of morbidity and mortality in diseases like aplastic syndrome [63]. Data on the application of thrombopoiesis-stimulating factors are limited to observational studies. A recently published study in refractory aplastic anemia showed response to eltrombopag in 11 of 25 patients [64]. Notably, 6 patients had improved in the erythroid cell lineage and 9 patients in the neutrophil counts. Application in single cases with dyskeratosis congenita or Diamond-Blackfan anemia were unsuccessful [65].

The current data in bone marrow failure syndromes may reflect the experiences in chemotherapy-induced thrombocytopenia. Only patients with residual megakaryopoiesis are likely to benefit from stimulation of thrombopoiesis.

### Chronic Liver Disease

Thrombocytopenia is a frequent complication of chronic liver disease. The degree of thrombocytopenia is proportional to the severity of the liver disease [66, 67]. Contributing factors are splenomegaly due to portal hypertension, decreased production of TPO, infection-induced bone marrow suppression in patients with hepatitis, and side effects of drugs such as IFN-α.

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Table 3. Randomized clinical trials with eltrombopag in cirrhosis

<table>
<thead>
<tr>
<th>Author / study</th>
<th>Patients</th>
<th>Control</th>
<th>New therapy</th>
<th>N</th>
<th>Response rate</th>
<th>No platelet transfusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>McHutchison, 2007 [57]</td>
<td>cirrhosis, hepatitis C</td>
<td>placebo</td>
<td>Elt 50&lt;sup&gt;d&lt;/sup&gt;</td>
<td>37</td>
<td>0 vs. 79&lt;sup&gt;e&lt;/sup&gt;</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>McHutchison, 2007 [57]</td>
<td>cirrhosis, hepatitis C</td>
<td>placebo</td>
<td>Elt 75&lt;sup&gt;d&lt;/sup&gt;</td>
<td>41</td>
<td>0 vs. 95&lt;sup&gt;e&lt;/sup&gt;</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>Afdhal, 2013 [56]</td>
<td>cirrhosis, elective surgery platelets &lt;50,000/μl</td>
<td>placebo</td>
<td>Elt 75</td>
<td>292</td>
<td>19 vs. 72</td>
<td>p &lt; 0.001</td>
</tr>
</tbody>
</table>

<sup>a</sup>Number of patients  
<sup>b</sup>% of patients with platelets ≥100,000/μl at the end of initial treatment phase.  
<sup>c</sup>% of patients with ≥50,000/μl for at least 6 weeks.  
<sup>d</sup>Number indicates the dose in mg.  
<sup>e</sup>Results for controls vs. results for new therapy.
Patients with thrombocytopenia have an increased risk for bleeding during and after invasive procedure. This may lead to cancellation or postponement of elective interventions [68]. In clinical trials of new drugs for hepatitis C, patients with platelets < 75,000/μl had been excluded [69]. Eltrombopag has been evaluated in two randomized clinical trials of patients with cirrhosis. Data are summarized in table 3. Data indicate that eltrombopag is effective in increasing the number of platelets in patients with liver cirrhosis either in preparation of elective surgery or initiation of antiviral therapy. In the latter indication, the need is dependent on the specific type of antiviral therapy. While IFN-α is associated with significant thrombocytopenia, this complication is less limiting for the new and more efficient antiviral drugs such as boceprevir, telaprevir, or others. In July 2013, the Committee for Medicinal Products for Human Use (CHMP) of the EMA has recommended the approval of eltrombopag for adults with chronic HCV infection and severe thrombocytopenia that prevents IFN-based therapy.

The protective effect of eltrombopag in preparation for elective surgery is clinically significant. However, the study was terminated early due to an increased incidence of portal-vein thrombosis, as compared to placebo. This complication also restrains the application of eltrombopag to other thrombocytopenic patients prior to elective surgery.

Disclosure Statement

The author declares no conflicts of interests with regard to the subject of this article.

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