Chronic immune thrombocytopenic purpura

New agents

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Summary
First generation thrombopoietic growth factors (rHuMGDF, PEG-rHuMGDF), investigated in the early 2000s, proved effective in increasing platelet count in normal volunteers, in thrombocytopenia due to chemotherapy and also in a few cases of immune thrombocytopenic purpura (ITP). These agents did not complete their clinical development since one of them induced antibodies in the recipients that cross reacted with endogenous thrombopoietin (TPO), thus causing thrombocytopenia. This promoted the ingenious design of a new generation of thrombopoietic growth factors having no sequence homology with natural TPO. The two main agents are romiplostim, a peptibody already approved for clinical use in USA and eltrombopag, a non-peptide, orally active small molecule. In open label and placebo-controlled trials both agents proved to predictably increase platelet count in normal volunteers and in patients with ITP. With appropriate dosages (1–10 μg/kg weekly subcutaneously for romiplostim; 50–75 mg/die per os for eltrombopag) a platelet increase becomes significant after 7–10 days and peaks between 10–14 days. By discontinuing treatment, platelet count returns to baseline level in 10–15 days. The response rate with both agents is above 70–80%, also in patients that had undergone several lines of treatment, or that have failed splenectomy. The response is maintained during the treatment, but is almost invariably lost even after several months of successful administration. Due to the lack of a curative potential and to the incomplete knowledge of long-term side effects, the place of these new drugs in the management of ITP is still unsettled and their use is best restricted to refractory patients or in preparation of splenectomy. It seems however that a new paradigm in the treatment of ITP has been established where the focus is not on reducing platelet consumption but on increasing platelet production.

Development of thrombopoietin mimetics

Recently, a new class of thrombopoietic growth factors having no sequence homology with natural thrombopoietin (TPO) has been tested in open label and in randomized trials in normal subjects (1, 2) and in patients with ITP (immune thrombocytopenic purpura) (2–6). One of these agents (romiplostim) was approved by Food and Drug Administration for clinical use last summer and a second molecule (eltrombopag) has completed its application for registration. These new agents engage TPO receptor on bone marrow megakaryocytes, greatly increasing platelet production. This capacity makes a new therapeutic strategy possible that is no longer exclusively based on reducing platelet destruction by immunomodulation/immunosuppression or splenectomy. The use of these new drugs represents the clinical application of recently delucidated pathogenetic mechanisms, showing that in most ITP cases there is an absolute or relative decrease in platelet production. Indeed, the paradigm that ITP was prevalently due to an accelerated peripheral platelet destruction mediated by auto antibodies against platelet membrane glycoproteins was challenged some 20 years ago by studying platelet kinetics with radio labeled autologous platelets (7, 8). These investigations firstly demonstrated that TPO patients may have a subnormal platelet turnover. It is now well documented that auto antibodies against platelet glycoproteins interfere with megakaryocyte maturation and platelet production (9, 10). Furthermore, TPO circulating levels found in patients with ITP are usually normal or only slightly elevated, but much less than those found in patients with thrombocytopenia due to megakaryocyte hypoplasia (11), indicating adsorption and destruction of TPO by the expanded megakaryocyte mass, thus creating a relative deficiency of TPO.

The search for a thrombopoietic agent began 50 years ago (12). But the first major advance in this search occurred only in 1992, with the identification and cloning of c-MPL, the cellular homologue of the Myeloproliferative leukaemia virus-derived oncogene, a leukaemogenic murine retrovirus that by infecting the mouse haemopoietic progenitors, caused their escape from haemopoietic growth factor-controlled proliferation and differentiation (13); c-MPL is present on multilineage human myeloid progenitors favouring their commitment towards megakaryocyte lineage. In 1994, the cloning of the gene for c-MPL ligand was reported (14, 15) and subsequently c-MPL ligand was identified as TPO (16). First generation of TPO growth factors were developed and tested in normal and thrombocytopenic patients (17). They included recombinant human TPO (rhTPO) (a full-length glycosylated molecule produced in a mammalian cell line, and a non-glycosylated truncated and pegylated recombinant human derivative of the molecule produced in Escherichia coli, called PEG-rHuMGDF (megakaryocyte growth and development factor).

Both molecules were able to increase platelet counts in normal subjects and in cancer patients treated with chemotherapy. A few cases of ITP were also successfully treated. Unfortunately, in a large study the administration of PEG-rHuMGDF in 538 healthy volunteers caused a prolonged thrombocytopenia in 13 subjects, due to the development of cross reacting antibody with endogenous TPO (17). This event led to immediate discontinuation of clinical development of these agents. However, the demonstration of their efficacy in increasing the
The platelet count in thrombocytopenic patients fastened the development of second-generation thrombopoietic growth factors without antigenic resemblance to natural TPO. These compounds, referred to as TPO mimetics, bind to and activate the e-MPL. At least three molecules have undergone clinical trials in primary ITP patients: (AMG 531) romiplostim, a TPO peptide mimetic called peptibody, and two orally active nonpeptide receptor agonists, eltrombopag (1, 5) and AKR-501 (7).

Clinical use of TPO mimetics

Given their pattern of response, with a platelet increase after 7–10 days from the start of therapy and a decrease to baseline count within 10–15 days after discontinuation, TPO mimetic agents are devoid of any curative potential and thus appear as a maintenance therapy tool, rather than a remission induction treatment. Excellent reviews, based on recently published controlled clinical trials are already available (18–21). Contrasting clinical application and mode of action of thrombopoietin mimetics with some therapeutic areas in ITP treatment that suffer major limitations might help to critically understand their therapeutic potential.

Unmet therapeutic goals

Notwithstanding a rich therapeutic armamentarium, including prednisone, intravenous immunoglobulin, splenectomy, anti-CD 20 antibodies and other various immunosuppressants, is available for ITP, these treatments are not always effective and in particular their toxicity is often unacceptable although justified in the more severe cases of the disease.

In the initial treatment, 10–15% of patients are resistant to prednisone, intravenous immunoglobulin (22–25) or high dose dexamethasone (26, 27) and may have a substantial bleeding risk, especially in case of trauma or surgery, including splenectomy. Nearly 70–80% of responders to initial treatment will develop chronic ITP with need of treatment in 50% of cases (28). In this group, the bleeding episodes may be severe with significant mortality caused by haemorrhage (29, 30). In chronic ITP (12 months from diagnosis) with a platelet count less than 20–30 × 10^9/l or requiring corticosteroids or immunosuppressants to maintain a safe platelet count, splenectomy remains the best therapeutic option and is usually offered to patients, because it provides a long-term benefit, with a complete (platelet count more than 100–150 × 10^9/l)

### Tab. 1 Data from peer-reviewed articles concerning the efficacy in term of platelet (PLT) increase in patients with idiopathic thrombocytopenic purpura (ITP) treated with TPO-agonists

<table>
<thead>
<tr>
<th>reference</th>
<th>type of study</th>
<th>drug</th>
<th>patients characteristics</th>
<th>intervention</th>
<th>efficacy (platelet count × 10^9/l)</th>
<th>rate response* n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3. Bussel et al. N Engl J Med 2007</td>
<td>double-blind, placebo-controlled</td>
<td>Eltrombopag</td>
<td>chronic ITP (at least 6 month-history); PLT at enrollment &lt; 30 × 10^9/l; at least one previous therapy 32% concomitant therapy; 47% splenectomized</td>
<td>27/29/27/26</td>
<td>≥50 at 43 day</td>
<td>3 (11) 8 (28) 19 (70) 21 (81)</td>
</tr>
<tr>
<td>4. Kuter et al. Lancet 2008</td>
<td>double-blind, placebo-controlled</td>
<td>AMG 531</td>
<td>median PLT: 16 × 10^9/l; range 2–31 × 10^9/l; 63% ≥ 3 previous therapy, 31% concomitant therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*only major responses considered; *excluding patients treated with low dosage in studies 1 (n = 12) and 3 (n = 39); BW: body weight

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or partial (platelet count more than 30–50 × 10^9/l) response in 60–80% of cases (31). However, there is a general tendency to avoid or to delay the surgical intervention for the fear of complications and the unpredictability of efficacy. Moreover, there is a subset of patients with contraindication to surgery for a concomitant disease or the presence of relevant risk factors. Chronic ITP patients rarely remit without splenectomy even during a prolonged follow up (32) and thus remain exposed to the toxicity of long-term immunosuppressive drugs. Furthermore, unfortunately, a significant proportion of patients (almost 15%) will relapse within a median of 33 months after splenectomy. There is no consensus on the best management for this group of patients. Some of them will eventually require some treatment for the occurrence of active bleeding or an unacceptable high risk of bleeding complications. Often these refractory patients are burdened with severe or even fatal infections, due to the multiple lines of immunosuppressive treatment (33–41). On the other hand, the risk of fatal bleeding (related to persistent severe thrombocytopenia) makes these treatments necessary so that the treating physician and his/her patient face a very difficult medical problem (42). Thus, it is evident that the actual standard therapeutic armamentarium for ITP suffers major limitations. Moreover, also some new approaches, such as the use of high dose dexamethasone (26, 27), the administration of anti-D immune globulin (43, 44), and the infusion of anti CD-20 antibodies (45,46) mainly aimed at avoiding or deferring splenectomy, have shown limited efficacy or may have been hampered by uncertainty on their long term safety or have been complicated by severe side effects (47).

**Therapeutic potential of TPO mimetics**

In the light of the above mentioned limitations, the introduction of second generation thrombopoietic growth factors may represent a novelty of great interest and holds a great promise in improving the treatment of ITP patients and their quality of life. The recently published randomized clinical trials with two of such agents, romiplostim and eltrombopag, clearly show that these agents are effective in increasing the platelet count in a large portion of splenectomized and not-splenectomized ITP patients (Tab. 1). Importantly, a reduction of the rate of bleeding episodes and of the use of concomitant therapy was also demonstrated in the active arms. However, some concerns should be raised: the studies showed that rebound thrombocytopenia, more severe than that at the beginning of treatment, may occur within 2–3 weeks after stopping these treatments and that bleeding risk is increased. This requires strict monitoring of patients. Furthermore, although thrombotic complications have not been reported at a significantly higher frequency compared to placebo, a few cases have been described that demand further assessment of this risk.

Moreover, a reversible increase of marrow reticulin was demonstrated in rare cases. Clinical trials for registration purpose do not have a sufficient statistical potency to fully evaluate the safety profile, and a stringent post-marketing survey will be required. At the moment, splenectomy remains a major therapeutic and often curative intervention in cases not responding to initial therapy. In our opinion, these new agents should be used in chronic patients meeting two conditions:

- failure or relapse after splenectomy (or with contraindication to surgery for older age and/or comorbidities);
- high risk of bleeding requiring active treatment.

In this situation a long term efficacy in the order of 70–80% of cases is expected whereas all available treatments (including low or minimal dose corticosteroids) appear burdened by relevant side effects or have limited long term efficacy, e. g. 20–30% for rituximab (45). The use of the new agents to defer splenectomy after 12 months from diagnosis, a time after which spontaneous remissions rarely occur, and/or in preparation of elective surgery or splenectomy (with appropriate thrombopoephilaxis once a safe platelet count is reached) should also be considered appropriate, but do not appear firmly established. These patients should be strictly monitored and frequent dose adjustments may be required to maintain platelet count within a therapeutic window between 30–50 and 200–300 × 10^9/l. Less restrictive indications have been issued by FDA for romiplostim, but only registered physician can prescribe the drug in USA. Waiting for decisions by regulatory European and Nationals agencies about the indications and limitations of the clinical use of TPO mimetic drugs, some open-label studies are ongoing in several European countries, recruiting ITP patients with refractory disease. Data from these trials in a large cohort of subjects will provide more useful evidence about long-term safety and efficacy.

**References**

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