



# First-line Idiopathic Thrombocytopenic Purpura Therapies – Benefits and Limitations

a report by

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Idiopathic thrombocytopenic purpura (ITP) is a primary acquired disease of adults and children characterised by transient or persistent decrease of the platelet count.<sup>1,2</sup> Bleeding may be severe and is usually related to the platelet count. When platelet count is lower than 20–30x10<sup>9</sup>/l, bleeding is manifested by variably extensive purpura and mucosal haemorrhages; occasionally, in the case of a much lower platelet count, this can be severe enough to cause a cerebral haemorrhage. Haemorrhagic deaths are reported in fewer than 1% of cases. When a safe platelet count (more than 20–30x10<sup>9</sup>/l) cannot be maintained, the mortality rate is greatly increased and proportional to the time at risk and age of the patient, reaching an age-adjusted death rate of 13/100 patient-years.<sup>3–6</sup>

The diagnosis is one of exclusion, based on the absence of additional clinical, haematological and routine laboratory investigations. The decrease in the platelet level is caused by autoantibody-mediated platelet destruction; however, in some cases a defective platelet production has also been demonstrated.<sup>7,8</sup> Moreover, the homeostatic mechanism of thrombopoietin (the growth factor regulating platelet production) seems to fail its scope in most ITP cases. This is now clearly shown by the efficacy of the second-generation thrombopoietin growth factors such as AMG 531 and eltrombopag, which increase the platelet count to a safe level in 70–80% of patients with ITP unresponsive to one or more lines of treatment and showing a defective production of endogenous thrombopoietin.<sup>9,10</sup>

Between 20 and 60% of adult patients presenting with newly diagnosed ITP will need prompt treatment with steroids (still the mainstay of initial treatment) with or without concurrent administration of high-dose intravenous immunoglobulin (IVIg) or anti-D immunoglobulin (anti-DIg) for their severe thrombocytopenia and/or the occurrence of haemorrhagic symptoms.<sup>11–13</sup> The major effort of initial treatment is to avoid the risk of major bleeding and to preserve the daily activities of the patient, including leisure and sporting activities. Usually, the response to initial treatment is of short duration, with fewer than 20% of patients maintaining a safe platelet count at six months post-discontinuation of corticosteroid administration. During this period, some long-lasting remissions may occur and some cases are apparently cured.

With the hope of deferring or avoiding splenectomy, which is the standard treatment for chronic ITP,<sup>14</sup> several attempts have been made to prolong the initial response using different approaches. These included repeated infusions of IVIg or anti-DIg; single or repeated courses of high-dose dexamethasone administered orally at 40mg/day for four days have also been tried.<sup>15</sup> However, repeated infusions of IVIg proved unfeasible due to high costs and a diminished efficacy over

time. The use of anti-DIg in order to delay or avoid splenectomy proved ineffective in at least two prospective studies.<sup>16,17</sup> The efficacy of high-dose dexamethasone in inducing a higher rate of durable remissions remains unsettled.

In a recent paper, Cheng and colleagues<sup>18</sup> reported their experience of treating 125 new cases of severe ITP with one course of high-dose dexamethasone. A good response was reached in 85% of patients and it was durable in up to 45%. In 50% of those relapsing, a second durable response was achieved with a second course. These promising results were confirmed in a subsequent multicentre prospective Italian study<sup>19</sup> in which high-dose dexamethasone was given every 14 days for up to four cycles, with an initial response rate of 85.6%. Results were better in patients receiving at least three courses of therapy. Relapse-free survival at 15 months was 81%. Unfortunately, in both trials no comparative arm was included, so these results require confirmation by randomised trials designed to compare high-dose dexamethasone with standard corticosteroids and including adequate follow-up.

Importantly, all of these treatments are burdened by significant levels of toxicity. The short- and long-term side effects of corticosteroids are well-known. What seems to be less recognised is that any dosage higher than the replacement dose, which is equivalent to 4–6mg/day of prednisone, may induce osteoporosis, myopathy, cushingoid features, metabolic effects, increased risk of infection and other adverse effects if taken for more than one year or in a much shorter

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time and administered at a higher dosage. Although IVIg and anti-DIg are considered safe, severe side effects have been described in a

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minority of patients treated for ITP with standard Ig (mainly thrombotic events and renal failure).<sup>20</sup> Very few cases of DIC associated with acute haemolysis and death have been documented in patients receiving anti-D.<sup>21</sup>

In summary, none of the current standard treatments is able to significantly modify the natural course of the disease by avoiding its chronic evolution. Many patients ultimately require more risky interventions such as splenectomy, which is carried out in 20–50% of cases presenting with severe ITP during the first year after diagnosis. Splenectomy, currently performed using a laparoscopic approach, provides long-term benefit for most, with a complete or partial response rate in more than 80% of cases and a low rate (15%) of relapse at a median of 33 months after surgery.<sup>14</sup> There is no consensus on the most appropriate management for those patients (around 5% of an initial cohort presenting with severe ITP) failing splenectomy and requiring active treatment to avoid bleeding.<sup>15</sup> On the other hand, the high risk of fatal haemorrhage in this subgroup, with a mortality rate for bleeding up to 2.2% in young patients and up to 47.8% in older patients, outweighs the increased risk of infective complications, which may be fatal, induced by most immunosuppressive treatments.<sup>6</sup>

An important novelty of the last decade is represented by anti-CD20

antibodies. In addition, there is a great expectation from the second generation of thrombopoietic growth factors such as AMG 531 and eltrombopag. The use of anti-CD20 antibodies in ITP patients has recently been reviewed.<sup>22</sup>

The administration of rituximab in patients with chronic ITP produces a good response in almost 60% of cases, with no significant difference between pre- or post-splenectomy patients. However, good long-term responses are observed in only 20% of initially treated cases, long-term safety data are lacking and some fatalities have been reported. Thus, currently, the administration of anti-CD20 antibodies before splenectomy should be considered only within controlled clinical trials or in selected patients.

Studies in phase II and III with second-generation thrombopoietin agonists showed that both AMG 531 and eltrombopag are able to increase platelet count in chronic ITP patients.<sup>23</sup> The peak platelet count is reached two weeks after the start of therapy and a return to basal level is normally seen two to three weeks after the end of treatment. A safe platelet count is obtained in almost 80% of cases, often with dose adjustment to obtain the desired increase. Headache and bleeding

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symptoms are the most frequent side effects observed. In two patients treated with AMG 531, an increase of bone marrow reticulin was seen. If the ongoing studies confirm these preliminary results, these and other similar agents under clinical development could be an alternative for refractory patients and for those waiting for splenectomy, sparing these patients more toxic treatments. ■

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