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# Treatment of chronic immune thrombocytopenic purpura in adults

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**Abstract** Until recently, the management of refractory immune thrombocytopenic purpura (ITP) was a real challenge as shown by the large variety of treatments proposed in both American Society of Hematology and the British Committee for Standards in Haematology guidelines published 10 and 6 years ago, respectively. However, as in the past 5 years, new therapeutic approaches including eradication of *Helicobacter pylori* in infected patients and rituximab have been proposed and the thrombopoietin-receptor agonists have been developed and licensed for ITP. It is likely that the therapeutic strategy of ITP will be profoundly modified and revisited in the next future. The purpose of this article is to discuss the impact and the place of these new therapeutic options into the whole treatment strategy of chronic ITP and to draw the perspective of new experimental therapies.

**Keywords** Immune thrombocytopenic purpura · Rituximab · Thrombopoietin-receptor agonist · *Helicobacter pylori* · Romiplostim · Eltrombopag

## Introduction

Primary immune thrombocytopenia (ITP), previously referred to as idiopathic thrombocytopenic purpura, is an immune-mediated acquired disorder characterized by isolated thrombocytopenia, defined as a peripheral blood

platelet count  $<100 \times 10^9/L$  in the absence of any other cause of the thrombocytopenia [1]. ITP is an orphan disease that can occur at any age with an overall incidence of 1.6 to 3.9/100,000 persons [2, 3]. In children, it is usually a self-limited disease which spontaneously recovers within a few weeks. In contrast, about 70% of adults remain thrombocytopenic after 6 to 12 months and thus develop chronic ITP. The signs and symptoms of ITP vary widely. Many patients have either no symptoms or minimal bruising, while others experience serious bleeding. The overall prognosis of ITP is good with a mortality rate less than 2% [4], but mortality can rise up to 10% in a subgroup of selected patients refractory to splenectomy [5].

ITP treatment has long been based mainly on empirical data with a few controlled studies [6]. Due to these limitations, it has been difficult to establish robust guidelines for the treatment of ITP. Nevertheless, ITP guidelines were produced by the American Society of Hematology (ASH) more than 10 years ago [7] and the British Committee for Standards in Haematology (BCSH) 6 years ago [8]. ASH and BCSH guidelines emphasize that the aim of treatment is primarily to prevent bleeding and avoid the side effects of therapy and not to normalize the platelet count. Usually, only patients with a platelet count of  $<30 \times 10^9/L$  and bleeding symptoms require treatment. Guidelines suggest corticosteroids as the first-line treatment. The use of IVIg or IV anti-D may be appropriate mainly in patients who present with severe bleeding symptoms. The effects of these first-line treatments are however often only transient, and splenectomy is proposed in both guidelines as the major second-line therapy. Patients who do not respond to splenectomy are defined as having refractory ITP.

Until recently, the management of refractory ITP was a real challenge as shown by the large variety of treatments proposed in both ASH and BCSH guidelines. However, as

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in the past 5 years, new therapeutic approaches (eradication of *Helicobacter pylori*, rituximab...) have been proposed and the thrombopoietin-receptor (TPO-r) agonists have been developed and licensed for ITP. It is likely that the therapeutic strategy of ITP will be profoundly modified and revisited in the near future. The purpose of this article is to discuss the impact and the place of these new therapeutic options into the whole treatment strategy of chronic ITP and to draw the perspective of new experimental therapies.

### ***Helicobacter pylori* and ITP**

*Helicobacter pylori* is a Gram-negative bacterium that colonizes the human stomach with a great variation of prevalence across the world. For example, the prevalence in Japan and Italy is greater than 50% while it is slightly less than 30% in France and even lower in the USA (about 20%). *H. pylori* infection has been suspected to be associated with a large spectrum of extra-intestinal diseases including various autoimmune disorders.

The relationship between *H. pylori* infection and ITP was first described 10 years ago by Gasbarrini et al. [9]. The rate of *H. pylori* infection in patients with ITP varies greatly from country to country, but this prevalence was not found different from that reported in the general healthy population matched for age and geographical area [10]. The clinical characteristics of *H. pylori*-associated ITP appear similar to those observed in non-infected ITP patients and are rarely severe.

The mechanism of *H. pylori*-induced thrombocytopenia is far from being established and many hypotheses have been raised [10]. One of them is molecular mimicry; *H. pylori* induce the production of a variety of antibodies, some of which could cross-react towards various platelet glycoprotein antigens. A protein named CagA, which is a virulence factor of *H. pylori*, can induce the production of antibodies that cross-react with a peptide specifically expressed by platelets of patients with ITP [11]. The proportion of CagA-positive strains of *H. pylori* varies depending upon geographic location [10]. This finding could explain why the association of ITP and *H. pylori* is stronger in some countries such as Japan and Italy.

Whether the eradication of *H. pylori* infection can increase the platelet count in patients with ITP is still a controversial issue [10]. Stasi et al. [12] conducted a systematic review of the literature including 1,555 patients. With a combination of amoxicillin, clarithromycin, and a proton pump inhibitor usually given for 1 to 2 weeks, an overall response defined by a platelet count of  $\geq 30 \times 10^9/L$  and at least doubling of the platelet count at baseline was observed in 50% of the cases. Reducing the analysis to the patients with a baseline platelet count  $\leq 30 \times 10^9/L$ , the

overall response rate was only 35%. The response occurred most commonly 2 weeks after the completion of eradication therapy whereas the long term response is not well known. The response rates were much higher in countries where the rate of *H. pylori* carriage is high. No severe side effects of the treatment occurred.

In view of these conflicting results, it is difficult to draw a consensual proposal concerning the interest of a systematic *H. pylori* screening in ITP patients. The screening would imply the use of the breath test or stool antigen tests as opposed to antibody testing in order to confirm *H. pylori* carriage. The non-invasiveness of diagnostic methods and the good cost/effectiveness ratio and safety profile of the standard eradication regimen should argue for a systematic screening of adults diagnosed with ITP and for an eradication treatment in *H. pylori*-positive patients. Ideally, it must be confirmed by a prospective randomized study that should include a large cohort of patients with various ethnical origins to be sure that the results could be adapted in all countries.

### **Rituximab**

Rituximab is a chimeric monoclonal anti-CD20 antibody that is currently indicated for the treatment of lymphoma. Because of its ability to deplete autoantibody-producing B lymphocytes and its apparently good safety profile, it has been used in patients with various autoimmune diseases such as lupus and rheumatoid arthritis [13]. Its efficacy in ITP was first reported almost 10 years ago [14] and it is now commonly used off-label in many countries in this setting, especially in patients who are refractory to splenectomy or in whom splenectomy is contra-indicated. A systematic review of the literature showed that rituximab resulted in complete response (platelet count of  $> 150 \times 10^9/L$ ) in 44% of patients and an overall response (platelet count of  $> 50 \times 10^9/L$ ) in 62% [15]. Responses generally occur after 1–2 weeks to 6–8 weeks.

An open non-randomized prospective study conducted in non-splenectomized patients with chronic ITP showed that, after 2 years of observation, 40% of patients had a platelet count of  $> 30 \times 10^9/L$  without treatment, suggesting that rituximab is an apparently safe splenectomy-avoiding option in some adults with chronic ITP [16]. A prospective randomized Italian study comparing dexamethasone alone with dexamethasone plus rituximab in adults with newly diagnosed ITP confirmed the interest of rituximab in non-splenectomized patients by showing a better response rate in the group of patients receiving rituximab with more than 60% of response after 2 years of follow-up [17].

However, despite these promising results, several points remain unresolved. Should the lymphoma regimen (i.e.,

375 mg/m<sup>2</sup>/week×4) be the one used for ITP ? What are the mechanisms of action of rituximab? Are there predictive factors of response? What is the long-term response and can we really cure ITP with rituximab? Is the treatment really safe?

Recent data provide some answers to these important questions.

Two open non-controlled studies used a fixed low dose of 100 mg weekly for four times in ITP [18, 19]. A complete and durable response was observed in about 60% of patients and efficacy of the treatment appeared comparable to that observed with the standard dose of the drug. Recently, a promising response was also reported with a low dose of veltuzumab, a new humanized anti-CD20 monoclonal antibody. Administered via only two intravenous or subcutaneous administrations, a sustained response was observed in 60% patients with chronic ITP [20]. However, the non-randomized design of these studies and the low number of patients included prevent one from drawing definite conclusion concerning the optimal dose of rituximab.

The mechanisms of action of rituximab are far from being completely known. However, Stasi et al. [21] demonstrated that there were several abnormalities of T cell subsets in ITP patients including an increase of the Th1/Th2 ratio and an expansion of oligoclonal T cells that could be reverted by a B cell depletion induced by rituximab. Stasi et al. [22] also showed that ITP patients had a reduced number and a defective suppressive capacity of T regs that could be restored after rituximab.

No clear predictive factors of responses of rituximab were determined, but younger age was associated with a better long-term good response [16] and early administration might have a better disease-modifying effect [21, 23]. It has been demonstrated that chronic ITP is associated with the expansion of oligoclonal T cells driving autoantibody production not suppressed by Tregs and with the expansion of self-reactive clones resistant to Fas-mediated cell death [21, 24, 25]. It is possible that oligoclonal T cells are less sensitive to rituximab that could argue for an early administration of this treatment in ITP.

The long-term efficacy of rituximab remains undetermined, but it has been shown that in a subset of long-term responders to rituximab about 20% of patients remained in remission after a follow-up of 5 years, suggesting that rituximab may definitely have a curative effect in ITP [26, 27].

Rituximab appears to have a good safety profile [16, 17, 28]. However, we cannot exclude that the long-lasting impairment of humoral immunity could lead to an increase risk of viral and/or bacterial infections. Hypogammaglobulinemia has been observed, particularly after multiple doses, in patients treated for rheumatic disorders [29]. Even if this risk is not well known in patients treated with rituximab for

ITP, multiple doses should be avoided in the case of relapse after a first cure and it is best to test the baseline immunoglobulins level prior to administering the treatment. Rituximab can induce hepatitis B virus (HBV) reactivation and fatal hepatitis has been reported. Rituximab is then contra-indicated in HBV-infected patients [30]. Several cases of fatal progressive multifocal leukoencephalopathy have been reported in patients with auto-immune diseases treated with rituximab, including one patient with ITP [31, 32]. An international registry could be useful to better assess the incidence of this very rare but life-threatening opportunistic infection.

### TPO-receptor agonists

ITP has long been considered to be only a matter of accelerated platelet destruction. However, a number of lines of evidence have come, showing that ITP is also a matter of impaired platelet production [33]. Suboptimal platelet production would be consistent with an important role for thrombopoietic agents in the management of ITP.

To date, two TPO-r agonists have been developed and licensed in ITP.

Romiplostim (AMG531, AMGEN) is a peptidobody consisting of two covalently linked carrier-Fc domains, each attached to a peptide containing many c-MPL-activating sequences. It is administered subcutaneously at weekly intervals. In pivotal studies conducted in splenectomized and non-splenectomized patients, overall response was observed in more than 80% of patients with chronic ITP [34]. Durable responses were seen in 61% of non-splenectomized patients and 38% of splenectomized patients. Platelet response was maintained by most patients during long-term treatment with romiplostim for up to 3 or 4 years in an open-label extension study [35].

In the USA, the FDA approved romiplostim as a long-term treatment for chronic ITP in adults who have not responded to standard treatments, such as corticosteroids, intravenous immunoglobulin, anti-Rho(D) immune globulin, or splenectomy. In Europe, the drug has obtained a license only in adult patients with chronic ITP who have failed to respond after splenectomy. Romiplostim may be considered as a second-line treatment for adult non-splenectomized ITP patients if surgery is contra-indicated.

Eltrombopag (promacta, GSK) is an oral, non-peptidic small molecule and a thrombopoietin-receptor agonist that is given orally once daily. In a randomized placebo-controlled trial compared with the effect with placebo, more than 70% of patients responded to the treatment over a 6-week period [36]. In an extended phase III study, almost 80% of patients maintained a platelet count of greater than  $50 \times 10^9/L$  for more than half their time in the study [37].

Romiplostim and eltrombopag appear to be well tolerated and no severe side effects were observed in the published studies including hundreds of patients. However, several potential adverse consequences of thrombopoietic growth factors are a matter of concern [33]. Thrombocytosis may occasionally occur with these drugs that could be associated with an increased risk of thrombosis. Reticulin deposition has been observed with both eltrombopag and romiplostim. It appears dose dependent [35]. In the absence of systematic bone marrow examination, its real incidence remains however unknown and could be underestimated. This side effect could be a problem in case of long-term use, particularly in young patients.

In summary, these agents appear unequivocally very active in ITP. How they impact the management of ITP remains to be seen, but they have some of the characteristics required for widespread usage: high rate of efficacy, low degree of toxicity. However, these treatments are costly and should be only considered as “supportive” therapy as due to their mechanism of action the platelet count usually decreases back to the pre-treatment level within 2 weeks following treatment withdrawal.

### Experimental therapies

With the better understanding of the pathophysiology of ITP, new therapeutic strategies are being developed. Among them, syk tyrosine-kinase inhibitors and humanized anti-CD40L monoclonal antibodies could be useful [38–40].

### Conclusion

Ten years ago, the ASH published ITP practice guidelines; we now benefit from new drugs tested in prospective clinical trials including multicenter, randomized studies. It is likely that the therapeutic strategy of ITP will be profoundly modified in the near future. It remains however difficult to propose a consensual and uniform therapeutic strategy at this stage as some of new treatments have only been recently licensed and pharmako-economics considerations could also influence our daily practice. Corticosteroids remain the first-line treatment and IVIg and anti-D are still indicated in case of severe bleeding manifestations since new drugs such as rituximab and TPO-r agonists do not increase the platelet count as quickly as steroids and immunoglobulin preparations do. Splenectomy has long been the “gold standard” second-line treatment for patients with persisting or chronic severe ITP, but it has now become obvious that an increasing number of both clinicians and patients are reluctant to consider/undergo splenectomy. Rituximab has become a possible alternative

to splenectomy, although the durability of response and its long-term safety is still a matter of debate and its use in an off-label setting has become a real issue in many countries now that new drugs have been licensed for ITP [41]. The efficacy of TPO-r agonists is unquestionable as clearly shown by several well-designed controlled randomized studies. These treatments however do not modify the natural course of the disease as they are not supposed to reverse the autoimmune process. They should therefore not be compared and balanced with other treatment strategies such as splenectomy and rituximab which aim to induce long-term remission or even to cure the disease [33]. Therefore, the use of these agents should be restricted to those patients who have a chronic refractory ITP [33, 41] according to the recent set of terminology criteria [1]. Whether the transient use of TPO-R agonist could be also helpful for the management of patients with severe persistent ITP still needs to be established as only a minority of these patients will eventually achieve spontaneous remission. Lastly, *H. pylori* eradication could be considered as rather anecdotal but, in view of the costless and safety profile of both the diagnostic methods and the eradication regimen, a systematic screening should be proposed to ITP patients at higher risk of *H. pylori* carriage, namely, living in countries with a high prevalence of Hp infection or above 50 years of age.

**Conflicts of interest** Bertrand Godeau is consultant for AMGEN France, Roche France and LFB (Laboratoire Français de Fractionnement et de Biotechnologies); he received research funds from AMGEN and Roche. Marc Michel has participated to scientific advisory boards from AMGEN and GlaxoSmithKline and has received fees as a speaker in satellite symposia for less than US\$ 10,000.

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