




# Proposal for a New Protocol for the Management of Immune Thrombocytopenia (ITP)

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## ABSTRACT

For many decades immune thrombocytopenia (ITP) was managed using therapies which had not undergone randomised clinical trials and included corticosteroids, immune suppression or splenectomy. These older therapies are associated with an increase in morbidity and mortality. These empirical therapies have variable efficacy and well-described side effects for many patients with minimal benefit to the patient. Over the past 10 years there has been a shift away from immune suppression and non-evidence-based therapies towards using treatments

with reduced or no immune suppression with an increasing reliance on the recently developed and approved thrombopoietin receptor agonists. The recent COVID-19 pandemic has made it more urgent that we develop non-immune suppressive strategies for ITP. In this commentary we describe our proposal for a contemporary approach to the management of ITP in adults that is based on our hospital practices and published guidelines.

**Keywords:** ITP; Corticosteroids; Immune suppression; Splenectomy; Thrombopoietin receptor agonists; COVID-19 pandemic; Contemporary approach

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### Key Summary Points

The management of immune thrombocytopenia (ITP) has, until the introduction of the second-generation TPO-R agonists, relied heavily on therapies which had not undergone randomised clinical trials.

Corticosteroids and immune suppression contribute to impaired quality of life for patients and poor clinical outcomes.

Current guidelines suggest the limitation of the use of first-line corticosteroids for 6 weeks or less in order to lessen the impact of corticosteroids on quality of life. They recommend to step to steroid-sparing agents such as TPO-RAs which have led to improved disease outcomes and quality of life.

However, there remains some confusion about TPO-RA switching and discontinuation.

Here we describe a protocol for improved ITP management including the switching and discontinuation of these agents.

Rituximab and immunosuppressants such as cyclosporin or vincristine are rather outrated.

## INTRODUCTION

Primary immune thrombocytopenia (ITP) is an acquired autoimmune disease affecting both children and adults [1–3]. The underlying cause is unknown but various factors including the development of autoantibodies against platelet glycoproteins, self-reactive T cells and other abnormalities within the immune system, and in some cases dysmegakaryopoiesis, lead to a reduction in the peripheral blood platelet count [4]. The thrombocytopenia that results may lead to bleeding in some patients.

For many decades ITP has been managed using therapies which had not undergone randomised clinical trials and included corticosteroids, immune suppression and splenectomy. These older therapies are associated with an increase in morbidity and mortality as shown by Portielje et al. [5]. These therapies have variable efficacy and well-described side effects for many patients with minimal benefit to the patient. Over the past 10 years there has been a shift away from immune suppression and therapies with limited evidence towards using treatments with reduced or no immune suppression with an increasing reliance on the more recently developed and approved thrombopoietin receptor agonists. The recent COVID-19 pandemic has made it more urgent that we develop non-immune suppressive strategies for ITP.

In this commentary we describe our proposal for a contemporary approach to the management of ITP in adults that is based on our hospital practices and published guidelines [6, 7]. The response definitions used are standard as defined by Rodeghiero et al. [8]. The response to treatment is, therefore, defined by the achievement of a platelet count greater than  $20\text{--}30 \times 10^9/\text{L}$  with a doubling of the baseline platelet count and disappearance of bleeding (if it occurred at diagnosis of the disease). The concept of refractoriness to the various treatments was also defined in the 2009 International Working Group Consensus [8]; this definition has not changed over the past 13 years. The period for defining non-response to the various treatments is indicated in Table 3 of the International Working Group Consensus and these times constitute the periods to follow when considering a treatment as non-effective.

According to the Spanish ITP Group (GEPTI), of which Dr. Tomás José González-López has been president since September 2021, the use of immunosuppressants (including the use of rituximab) [9] in times such as the current COVID-19 pandemic should be avoided because of possible severe infection caused by SARS-CoV-2. Outside of this pandemic, current Spanish guidelines [10] recommend these drugs as third-line treatment options after the use of corticosteroids, intravenously administered

immunoglobulin, thrombopoietin analogues (TPO-RAs; romiplostim, eltrombopag, avatrombopag) and Syk inhibitors (fostamatinib).

Finally, it should be noted that the current price of the two drugs currently launched on the market for the treatment of ITP (fostamatinib and avatrombopag) is lower than that of the two TPO-RAs traditionally available on the market (romiplostim, eltrombopag). The savings that their use entails compared to other therapeutic alternatives represents an economic relief for public health systems such as ours from Salud CastillayLeón (SACYL).

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

## FIRST-LINE TREATMENT FOR ITP

Prednisone (or prednisolone) is used first-line at a dose of 1 mg/kg/day for 1 week. If no response is seen after 1 week, a second week of treatment may be administered at a dose of 1.5 mg/kg/day. If there is no platelet response after this second week, the corticosteroids should be tapered and stopped.

Boluses of dexamethasone 40 mg daily for 4 days, for up to four cycles every 28 days may be used as a therapeutic alternative to prednisone. The time to consider response to the aforementioned treatment is defined in the consensus by Rodeghiero et al. [8].

Intravenously administered immunoglobulin (IVIg) is considered first-line treatment but is reserved in ITP for those patients who are bleeding or at high risk of bleeding. The dose to be administered (2 g/kg weight) can be given according to two therapeutic schemes: 1 g/kg weight/day for two consecutive days or 0.4 g/kg weight/day for 5 days of treatment. Efficacy is similar in both schemes. Note the UK guidance is 1 g/kg and seldom 2 g because the effect is similar.

Platelet transfusion is only used in ITP where there is life-threatening bleeding or there is a high risk of bleeding. In emergency situations we may use romiplostim 10 µg/kg/week as a therapeutic alternative to the use of IVIg [11].

## SECOND-LINE TREATMENT FOR ITP

Even though the international guidelines (IWG) [7] support the use of TPO-RAs or fostamatinib as second-line treatments, the Spanish guidelines only recommend the use of any TPO-RA (eltrombopag, romiplostim or avatrombopag) individually in second-line therapy.

Following the Spanish guidelines [10], we recommend using any of the three TPO-RAs (eltrombopag, romiplostim or avatrombopag) as second-line treatment. If, after using a TPO-RA, it needs to be discontinued because of refractoriness (no response) or grade 3–4 serious adverse events (SAEs), any of the other two TPO-RAs may be chosen [12, 13] since the efficacy rates for all three TPO-RAs are similar and the adverse effects will most likely subside after the switch [14].

When it is necessary to consider switching between TPO-RAs because of lack of efficacy of a first TPO-RA, we will preferably choose avatrombopag as a second TPO-RA given the excellent results reported at ASH 2021 by Al-Samkari and colleagues [15].

## THIRD AND SUBSEQUENT TREATMENT LINES FOR ITP/REFRACTORY PATIENTS

In third line we recommend the use of fostamatinib.

When TPO-RAs (eltrombopag, romiplostim or avatrombopag) in monotherapy and fostamatinib fail, we would offer the patient entry into a clinical trial or, failing that, we would use combinations of treatments. Thus, our protocol recommends combinations of two TPO-RAs or TPO-RA plus low dose MMF after a lack of response to two or more of these in monotherapy. Good responses have been observed with the combination of two TPO-RAs even when the patient has not responded to each of these separately.

Among the treatments for refractory patients, we cannot clearly recommend any combination given its lesser efficacy in the short term and, above all, in the long term, and its

greater toxicity. However, according to the International Guidelines [6], we recommend the combination of a TPO-RA plus low doses of corticosteroids.

If all the aforementioned treatments fail, or lead to serious adverse effects unacceptable to the patient, the haematologist may choose between

- Rituximab ± low dose corticosteroids
- Mycophenolate mofetil (MMF) alone or in combination
- Azathioprine alone or in combination
- Splenectomy
- Others (if the above fail or are not recommended): monotherapy or combinations of cyclosporin A, vinca alkaloids, etc.

## CONCLUSION

New drugs, including avatrombopag and fostamatinib, have been developed that increase our arsenal of therapeutic options for this disease. Nevertheless, despite the publication of various national and international guidelines, many haematologists do not know which drug to choose among robust therapies in many therapeutic situations e.g. what to do when a former TPO-RA has failed, when to use fostamatinib, etc.

Here we describe our Burgos protocol which we use in our ITP practice in our institution as a treatment proposal that may support how to address ITP treatment in early 2022 in Europe.

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**Compliance with Ethics Guidelines.** This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

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