An Pediatr (Barc). 2018;xxx(xx):xxx–xxx

analesdepediatría

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SPECIAL ARTICLE

Controversies in the treatment of paediatric immune thrombocytopenia☆

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Received 10 May 2018; accepted 22 June 2018

KEYWORDS
Immune thrombocytopenia;
Paediatric;
Childhood;
Thrombopoietin analogues

Abstract Immune thrombocytopaenia (ITP) is a relatively common disorder in childhood. Although it usually achieves spontaneous remission at this age, the management of persistent or chronic ITP in children is still controversial. The aim of this article is to address current controversies related to the treatment of persistent, chronic, and refractory ITP in children, including the role of rituximab and splenectomy, as well as focusing on a new approach with thrombopoietin receptor agonists (TPO-RAs). Eltrombopag and romiplostim are safe and useful drugs for paediatric ITP. These two TPO-RAs might delay surgery and other treatments such as rituximab. However, the potential side effects described in adult patients should be considered. Paediatric patients with refractory ITP, undergoing new treatments, should be supervised in specialised centres.

PALABRAS CLAVE
Trombocitopenia inmune;
Pediatría;

Controversias en el tratamiento de la trombocitopenia inmune pediátrica

Resumen La trombocitopenia inmune (PTI) es una entidad relativamente frecuente en pediatría. Aunque su evolución suele ser favourable en la mayoría de los casos, el manejo de aquellos pacientes en los que la enfermedad persiste es muy controvertido. Este artículo

☆ Please cite this article as: Berrueco R, Dapena JL, Sebastián E, Sastre A. Controversias en el tratamiento de la trombocitopenia inmune pediátrica. Ann Pediatr. 2018. https://doi.org/10.1016/j.anpedi.2018.06.010

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Infancia;
Análogos de la trombopoyetina

pretende, a través de una revisión de la literatura más reciente, responder a aspectos relacionados con el tratamiento de la PTI persistente, crónica y refractaria durante la infancia, haciendo especial énfasis en el papel del rituximab, la esplenectomía y los análogos de la trombopoyetina (ar-TPO) en la infancia. La aparición de los ar-TPO (eltrombopag y romiplostim) amplía el arsenal terapéutico de la PTI pediátrica. Además, tras haber demostrado un perfil de seguridad adecuado en ensayos clínicos, retrasa la indicación de esplenectomía o el uso de tratamientos asociados a mayor riesgo de complicaciones, como rituximab. No obstante, se recomienda que su manejo sea supervisado por centros con experiencia de cara a monitorizar complicaciones potenciales a medio y largo plazo ya descritas en el paciente adulto.

Introduction

Immune thrombocytopaenia (ITP) is an acquired immune-mediated disorder characterised by an isolated thrombocytopaenia secondary to destruction of platelets mediated by autoantibodies. Unlike adults, most paediatric patients have a benign course that is self-limiting and a lower risk of bleeding. However, the disease may become chronic in up to 20% of patients. Based on the duration of the disease, ITP is classified as newly diagnosed (<3 months' duration), persistent (3–12 months) or chronic (>12 months).[1]

Although ITP is relatively frequent in children current diagnosis and treatment guidelines[1–3] have not succeeded in establishing the optimal treatment strategy at certain stages of disease. The most controversial aspects concern to the management of patients with persistent or chronic ITP and children who do not respond to first-line treatment (regardless of disease duration).

The development of new drugs indicated for its use in children motivated us to write this article, where we attempt to address several issues in the treatment of persistent, chronic and refractory ITP in children, and the position of these novel agents in the treatment algorithm.

How are persistent, chronic and refractory ITP defined and diagnosed in the paediatric age group?

ITP is defined as persistent when thrombocytopaenia continues after 3–12 months from the initial diagnosis.[2,4] However, there is less agreement in the definition of refractory ITP. In adults, refractory ITP is defined as a disease that does not respond or relapses after splenectomy, a criterion that cannot be applied to the paediatric population, since surgery is not considered a second-line treatment in many cases.[5] Thus, it has been proposed that this definition includes children with significant bleeding that do not respond to first-line treatment or without significant bleeding in whom the primary objective of treatment is to improve the quality of life.

We ought to highlight that in either case, and regardless of whether the patient has ever experienced spontaneous remission, there is still a high probability that spontaneous remission will occur within a year from diagnosis.[6] This is important in regard to following steps as surgical treatment (splenectomy) or treatments associated with a higher incidence of complications (such as immunodeficiency secondary to use of rituximab) should be avoided if possible.

At any rate, diagnosis needs to be confirmed before developing a treatment plan[5] (Fig. 1). In infants aged <1 year, the possibility of congenital thrombocytopaenia or ITP secondary to an underlying immunodeficiency must be contemplated. A history of recurrent infection or the presence of concomitant immune-mediated cytopenias should lead to suspicion of a primary immunodeficiency. Evaluation by a clinical immunologist is advisable in these cases. It is also important to take into account that ITP may be secondary to other autoimmune disorders. Thus, systemic lupus erythematosus, antiphospholipid syndrome and other autoimmune disorders of connective tissue should be ruled out in patients with compatible presentations (regardless of the duration of disease) and once a year, at minimum, in all patients with chronic ITP (especially in female adolescents or after a prolonged course of disease).[1,3]

Which approach is most appropriate for management of persistent and refractory ITP in children?

When it comes to paediatric patients with ITP, the most important step prior to initiating treatment is to assess whether it is justified by haemorrhagic manifestations. Thus, treatment should be reserved for patients with active bleeding (excluding exclusively cutaneous bleeding). On the other hand, prevention of bleeding in asymptomatic patients would only be justified in the case of surgical intervention or if the clinician in charge believes that there is a high risk of bleeding associated to the physical activity of the child. Other factors, such as the circumstances of the family (parental anxiety or socioeconomic status, among others) or the quality of life of the patient may also be taken into account in treatment planning, always balancing the risks and benefits of treatment.[7]